INDOOR NITROGEN DIOXIDE EXPOSURE AND RESPIRATORY ILLNESS IN CHILDREN

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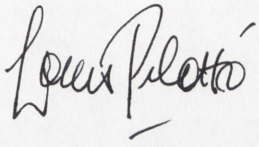
This is to confirm that, unless otherwise stated, this thesis is entirely my own original work, conducted through the National Centre for Epidemiology and Population Health of The Australian National University.



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ABSTRACT

Nitrogen dioxide (NO_2) levels were monitored during winter in 41 classrooms in 8 schools, four of which used unflued gas heating and four of which used electric heating. Each classroom was monitored daily with 6-hour passive diffusion badge monitors over nine alternate weeks, and concurrently with hourly monitors over two of those weeks, between April and September 1992. Children living in homes with gas appliances were also monitored daily over 4 days during times of gas use. Monitoring aimed to reflect spike daily levels of NO_2 exposure. The maximum hourly concentrations found in unflued gas heated classrooms exceeded the World Health Organization's recommended goal on twenty-three percent of measured days, and the daily timed-average concentrations exceeded the one hour goal in nine percent of unflued gas appliance homes. Satisfactory respiratory system diaries were provided by parents on 598 of the pupils, aged from 6 to 11 years, of whom 29 percent were excluded because of parental smoking at home or failure to provide information on this or gas use at home. Children from gas heated classrooms or gas appliance homes with mean daily timed-average nitrogen dioxide levels above 0.04 ppm either at school or at home were considered to be exposed. This level was associated with spike exposure levels of the order of 0.08 ppm or higher compared to background levels of the order of 0.02 ppm or lower in non-gas atmospheres. This ratio of spike to background level is consistent with those used in animal studies that showed a significant increase in mortality following bacterial challenge in mice exposed to spike levels of nitrogen dioxide. The proportions of exposed children with non-zero symptom "rates" for the presence of a cold and absenteeism were significantly higher than those for controls. As well, exposed children had significantly higher non-zero "rates" for sore throat, cough with phlegm and lower respiratory tract episodes involving cough with phlegm. Sensitivity analysis suggests a dose-response effect with increasing levels of spike nitrogen dioxide exposure. The

level of 0.04 ppm, above which a significant increase in symptomatology was found, represents a level of concern that is considerably lower than the World Health Organisation's and National Health and Medical Research Council's recommendations. A maximum one-hour goal of 0.08 ppm is recommended for school classrooms and a new goal time of 6 to 8 hours is suggested.

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CHAPTER 1

INTRODUCTION

The association between extremes of ambient (outdoor) air pollution and adverse health effects has been well documented.[1,2,3] Stern and colleagues described conditions reported by the Roman philosopher Seneca as far back as 61 AD:

> As soon as I had gotton out of the heavy air of Rome and from the stink of the smoky chimneys thereof, which, being stirred, poured whatever pestilential vapors and soot they had enclosed in them, I felt an alteration of my disposition.[1]

More recently, three notable episodes of air pollution associated with illness and death have occurred this century.[2] In December 1930 in the Meuse valley in Belgium, atmospheric conditions over five days resulted in the illness of hundreds of people, with sixty deaths from respiratory complications thought to be caused by waste gas from the many nearby factories. Similar conditions involving industrial emissions of sulphur dioxide and particulate matter at Donora in the United States of America (USA), in October 1948, resulted in the illness of forty-two percent of a population of fourteen thousand. Eighteen people, all aged over fifty, died, fourteen of whom had a previous history of respiratory illness. Finally, the London fog of 1952 resulted in approximately four thousand deaths thought to be due to the irritants derived from coal combustion. It was this latter event that led to the landmark legislation in the United Kingdom (*The Clean Air Act of 1956*[3]) and led to the first investigations into the extent of air pollution in Australia.

Since that time many outdoor air pollutants have been linked to adverse health effects and Abramson and Voigt, in a comprehensive review of this link, concluded that "respiratory symptoms are associated with sulphur dioxide, nitrogen dioxide, ozone and suspended particulates." and that "Decrements in

lung function have been associated with nitrogen dioxide and ozone."[4] To protect against these effects, air quality guidelines have been introduced aimed at minimising possible harm occurring to those exposed. As a result, the levels of many ambient pollutants have been reduced and the hazards associated with outdoor exposure have correspondingly diminished.[5]

In developed countries, however, little time is spent outdoors. Most pollutant exposure occurs inside, and the majority of pollutants are generated from indoor sources. Although research has increased in recent years, the association between indoor exposure to these agents and health effects is unclear. This lack of clarity is related to inaccurate classification of subjects due to absent or limited measurements of exposure and inaccurate recording of illness occurrence due to bias. Results, based on the use of retrospective health questionnaires, may be biased by whether or not subjects are ill or have symptoms at the time of questionnaire completion.[5] Newly evolving technology, however, is permitting accurate measurement of atmospheric exposure to many pollutants with consequent improvements in classification of exposure status. This has led to increased interest and activity into indoor air research, with the hope of overcoming previous limitations and of finding consistent patterns of effect.[5]

In pursuing such research, however, one needs to consider air quality guidelines. It has generally been recognised that some groups of individuals will be more susceptible than others to particular pollutants, and guidelines aim to protect these individuals.[6] It is the research evidence derived from such groups that drives the setting of air quality standards, and research should be aimed at providing information to assist in this process. It is important, therefore, to include susceptible subjects in future study designs.

This is the background against which this epidemiological study into the association between childhood respiratory illness and indoor exposure to one

particular pollutant, nitrogen dioxide (NO_2), was developed. A review of the literature had not revealed a clear association between the two, for the reasons already mentioned. It was important, therefore, to design a study that could circumvent the problems identified.

Children were chosen as study subjects because they were a recognised susceptible group.[7,8] Aged from six to eleven years, they were selected from eight schools, chosen on the basis of the presence or absence of unflued gas heaters, a known source of NO_2. A prospective design was developed to reduce bias related to the retrospective collection of health data. This involved the use of daily respiratory diaries completed by parents, rather than the documentation of past histories, to determine illness. An instrument, the passive diffusion badge monitor, with the capacity to accurately measure indoor concentrations of NO_2 over time, was chosen for air measurement. Using this instrument, various protocols were tested in a 1991 pilot study to determine the best method of accurately classifying the exposure status of the children involved. This formed the basis for the air monitoring protocol used in the main study conducted in 1992.

This thesis first examines the literature and its influence on the selection of the study design, followed by a description of the contribution of the pilot study to the development of the main study protocol. Ensuing chapters discuss and describe the main study protocol in detail, explore the patterns of indoor NO_2 concentrations, and follow with a detailed examination of their association with adverse health effects. Finally, the results are reviewed in the light of current air quality standards, their public health implications are explored and suggestions for future research direction are given.

CHAPTER 2

LITERATURE REVIEW

Nitric oxide, a precursor to NO_2, is formed by the burning of fossil fuels outdoors, and tobacco smoke and the use of gas-fired appliances indoors.[9] After formation, it undergoes rapid oxidation to produce NO_2, that remains in the environment and is available for human exposure.[10] This chapter reviews epidemiological studies that have examined the association between NO_2 exposure and childhood respiratory illness, and discusses a number of methodological problems. The toxicity of different exposure patterns to NO_2 in animal studies are reviewed. Infectivity and host defences are discussed to link toxicity in human and animal models. Controlled human exposure studies are also reviewed because they provide information about the levels of exposure that are associated with health effects under experimental conditions. Investigations that identify the concentrations of NO_2 experienced in Australian homes and classrooms are included for comparison with recommended levels. Finally, the contribution these issues make to the setting of air quality guidelines are discussed and the rationale for the study design and reason for proceeding with a pilot study prior to the main study are explained.

CHILDHOOD EPIDEMIOLOGICAL STUDIES

Many childhood epidemiological studies have been undertaken. These have been grouped according to the methods used to classify exposure, which provide key issues for discussion in the methodological considerations that follow. Ambient NO_2 levels, gas cooking at home, and indoor NO_2 levels have all been used for this purpose. Studies of the association between exposure, based on these methods, and respiratory illness have yielded mixed results.[11]

Ambient (outdoor) exposure studies

All studies that relied on ambient NO_2 levels as measures of exposure found some relationship between exposure and respiratory illness (Table 2.1).

Shy and colleagues conducted a 24 week prospective study of acute respiratory illness among 968 families living in an area of high NO_2 exposure, an area of increased exposure to suspended particulates and in two control areas. These families included 987 second grade school-children. Biweekly postcards were used to determine illness history, according to a "yes" or "no" response to the question "Did anyone in your household have a new cold or sore throat in the past two weeks?" Affirmative responses were followed up with a telephone call to ascertain age, sex and severity of illness of household members. An excess of respiratory illness was found in second grade school-children exposed to high levels of ambient NO_2. However, the contribution of NO_2 to illness production is unclear. Average 24 hour concentrations of NO_2, total suspended particulates, suspended nitrates and sulphates were measured during the study period in all areas. Exposure to NO_2 was highest in the high NO_2 area. However, exposure to suspended sulphates, reflecting emissions associated with nearby sulphuric acid manufacture, was also highest in the high NO_2 area. Also, the concentration of suspended particulates in the high particulate area was only marginally higher than in the high NO_2 area. This complex mixture of pollutants in the high NO_2 area makes it difficult to attribute the excess illness in this area to NO_2 alone.[12] This study, referred to as the Chattanooga school children study, has been criticised in assuming to be able to distinguish the relative exposure contribution of NO_2 from other pollutants.[9]

Pearlman and co-workers used a retrospective questionnaire in 3217 children to determine the presence of bronchitis, croup and pneumonia over the previous three years. Bronchitis only was found to be significantly increased in the first and second grade school-children exposed to elevated

ambient NO_2 levels during that period. Ambient levels in this study were determined in three geographical areas, chosen to represent a pollutant gradient. This provided high, intermediate and low NO_2 areas. Total suspended particulates and suspended sulphates were also measured and found to be highest in the high NO_2 area. As well, the 24 average levels of NO_2 in all areas were relatively low. This again makes it difficult to attribute increased illness to NO_2 alone.[13]

Mostardi et al., using both a cross-sectional study design involving a modified Tucson Longitudinal Population Study Questionnaire and a longitudinal design with daily diaries to record symptom occurrence, found an increased incidence of respiratory symptoms in more highly polluted areas. Children from two schools were involved in this study, one of which was located near several large industrial plants. Children from this school were exposed to higher levels of sulphur dioxide and total suspended particulates, as well as higher levels of NO_2.[14,15] It was not possible to determine the contribution of individual pollutants from this complex mixture to the higher rate of illness production.

Love and co-workers replicated the Chattanooga study using a longitudinal design and found increased respiratory illness in children in more highly exposed areas. This occurred after NO_2 pollution had been substantially reduced in all areas since the previous study. Increased illness was associated with current high short-term concentrations of NO_2 even though the average concentrations were little higher than average concentrations in the low pollution area. Sulphur dioxide was not monitored during this study. Importantly, the authors make the point that it was not possible to attribute illness excess to specific pollutants.[16]

Table 2.1 Studies that examined the relationship between ambient (outdoor) nitrogen dioxide levels and respiratory illness in children

Design	NO_2 Exposure	Symptom measure	Results	Reference
Longitudinal N=987 children in 968 families	Ambient average conc. 0.043 ppm to 0.109 ppm	Bi-weekly postcard; phone call if new cold or sore throat	Excess illness in children exposed to high NO_2 areas	Shy et al. 1970 (12)
Cross-sectional N=3217 infants or 1st and 2nd grade school children	Ambient average conc. 0.043 ppm to 0.083 ppm for 2-3 years	Questionnaire for bronchitis, croup and pneumonia; ie. lower respiratory tract.	Bronchitis increased in children and infants exposed to elevated NO_2	Pearlman et al. 1971 (13)
Cross-sectional N=299 children aged 10-11yrs	Ambient average conc. 0.014 ppm to 0.027 ppm	Questionnaire based on Tucson Longitudinal Population Study Ques.	Higher symptoms associated with higher polluted areas (NO_2 and SO_2)	Mostardi et al. 1981 (14)
Longitudinal N=299 children aged 10-11yrs	Ambient average conc. 0.014 ppm to 0.027 ppm	Daily diaries used for symptoms; given by teachers	Higher incidence of cough, sore throat and runny nose in higher polluted areas	Mostardi et al. 1981 (15)
Longitudinal N=2727 children and adults	Ambient 24hr. mean conc. 22-91 $\mu g/m^3$	Bi-weekly phone data for symptoms	Excess resp. illness in children in higher NO_2 areas	Love et al. 1982 (16)
Longitudinal N=4898 children aged 0-12yrs	Ambient mean NO_2 of 0.049 ppm	Bi-weekly phone data for symptoms and illness	A U-shaped relation was found for illness and NO_2 conc.	Harrington et al. 1985 (17)
Longitudinal N ranged from 304 to 701 on yearly basis	Ambient mean NO_2 of 0.02 to 0.06 mg/day per $100cm^2$	Questionnaire every summer for symptoms	Symptoms more prevalent in children more heavily exposed to pollution including NO_2 and SO_2	Kagamimori et al. 1986 (18)

Harrington and Krupnick, using data collected biweekly by telephone for symptoms and illness in children aged up to twelve years, found a U-shaped relationship between ambient NO_2 levels and respiratory illness.[17] No explanation has been found for this unique result. It has not been replicated in other studies and would appear to be biologically implausible, since increasing illness occurrence would be expected with increasing levels of exposure. However if such a curve were to exist, Abramson and Voigt suggest this could account for some of the negative findings from studies that used dichotomous exposure categories.[4]

Kagamimori and colleagues found a higher prevalence of respiratory symptoms in atopics, that is, children with a positive reaction to house dust extract, and school children more heavily exposed to air pollution from steam power stations. Both NO_2 and sulphur dioxide (SO_2) were more highly correlated with prevalence rates for respiratory symptoms than total suspended particulates. However, inconsistencies existed. For example, both NO_2 and SO_2 were highly correlated with subacute cough and phlegm, while NO_2 was highly correlated with wheezing. Yet, SO_2 was highly correlated with "respiratory illness with absence".[18]

It is clear that the contribution of NO_2 to illness production in these studies is uncertain. This is supported by Mostardi, who suggests that it was impossible to determine which ambient pollutant was responsible for any health effect in outdoor studies, because of the large number of pollutants involved.[14] This severely limits any interpretation that can be made about the contribution of NO_2 to adverse health effects in the studies described.

Gas cooking exposure studies

The use of gas cooking at home as a surrogate for NO_2 exposure in epidemiological studies mainly occurred prior to technology that allowed

accurate objective measurement of the indoor environment. A number of studies, relying on the presence of gas cooking at home to classify exposure, found a positive relationship between gas cooking and respiratory illness in children (Table 2.2).

Melia[19,20] and Florey[21] and their colleagues found a positive relationship between gas cooking at home and respiratory symptoms and illness, including excess cough, colds going to the chest and bronchitis. Melia's earlier study[19] did not control for parental smoking, but this was corrected in later studies.

Speizer and co-workers, using physician diagnosed bronchitis and a history of respiratory illness, found a significant positive association between gas cooking and a history of respiratory illness before the age of two.[22]

Dodge employed a modified Tucson Longitudinal Population Study questionnaire for asthma, sputum, cough and wheeze. The prevalence of cough only was found to be significantly higher in homes that used gas cooking.[23]

Ekwo et al. found that hospitalisation for respiratory illness before the age of two was positively associated with gas cooking at home. Such an association was not found for coughs with colds in children.[24]

Houthuijs[25] found an increased prevalence of respiratory symptoms associated with the use of unvented geisers in the kitchen, while Melia[26] found a positive association between gas stoves and wheezing, bronchitis, cough in the morning and colds that went to the chest in certain ethnic groups, namely "Afro-Caribbeans and whites".

Table 2.2 Studies that found a positive relationship between gas cooking at home and respiratory illness in children

Design	Symptom measure	Results	Reference
Cross-sectional N=5758 children aged 6 to 11yrs	Retrospective questionnaire for symptoms in the previous year; smoking not controlled	Excess cough, colds going to the chest and bronchitis in gas cooking homes	Melia et al. 1977 (19)
Cross-sectional (N=4827) and longitudinal (N=2408) aged from 5 to 11yrs	Questionnaire as above but smoking was included	Relative risk was variable - but mostly an increased risk of one or more symptoms with gas cooking	Melia et al. 1979 (20)
Cross-sectional N=808 children aged 6 to 7 yrs	Symptom Ques. based on Medical Research Council Questionnaire (MRCQ)	Positive association between gas cooking and respiratory illness	Florey et al. 1979 (21)
Cross-sectional N=8120 children aged 6 to 10yrs	Questionnaire for Dr diagnosed bronchitis and h/o serious respiratory illness before aged 2 and in the previous year	Significant association between gas cooking at home and respiratory illness before the age of 2yrs	Speizer et al. 1980 (22)
Cross-sectional N=676 children aged 8 to 12yrs	Questionnaire for asthma, sputum, cough, and wheeze	Prevalence of cough was significantly higher in homes with gas cooking	Dodge 1982 (23)
Cross-sectional N=1138 children aged 6 to 12yrs	Modified American Thoracic Society Questionnaire (ATSQ)	Hospitalisation before the age of 2 was associated with gas cooking at home	Ekwo et al. 1983 (24)
Cross-sectional N=630 children aged 6 to 9yrs	World Health Organization Questionnaire for respiratory symptoms	Gas use at home associated with an increased prevalence of resp. symptoms	Houthuijs et al. 1987 (25)
Cross-sectional N=4815 children aged 5 to 11yrs.	Retrospective questionnaire for respiratory symptoms in ethnic groups.	All respiratory conditions (except asthma) were most prevalent in Afro-Caribbeans and whites	Melia et al. 1988 (26)

In contrast to these studies, a number failed to demonstrate a positive association (Table 2.3). Keller and co-workers, following a twelve month longitudinal study involving 441 families, found gas cooking was not associated with an increase in respiratory illness in either adults or children.[27]

Table 2.3 Studies that found no relationship between gas cooking at home and respiratory illness in children

Design	Symptom measure	Results	Reference
Longitudinal N=1952; including 776 children	Bi-weekly phone data from each household	No association found between gas cooking and respiratory illness in children or adults	Keller et al. 1979 (27)
Cross-sectional N=4070 children aged 5 to 14yrs.	American Thoracic Society Ques. for respiratory symptoms and illness (ATSQ)	No significant association between gas cooking and symptoms or illness	Schenker et al. 1983 (7)
Cross-sectional N=10106 children aged 6 to 9yrs	Retrospective questionnaire for symptoms and illness	No significant relation between respiratory illness and gas cooking at home	Ware et al. 1984 (28)
Longitudinal N=4898 children aged up to 12yrs	Bi-weekly telephone data for symptoms and illness	Respiratory illness was not related to gas cooking at home	Harrington et al. 1985 (17)
Longitudinal N=1565 infants in their first year of life	Hospitalisation and recall of symptoms in the previous year	No significant association was found. Trends did occur	Ogston et al. 1985 (29)

Schenker and colleagues, in a cross-sectional study of 4070 children aged from 5 to 14 years, found that the use of gas for cooking at home was not an independent risk factor for either respiratory symptoms or illness.[7]

Of particular significance, Ware and colleagues[28] expanded the cohort used in Speizer's[22] study and failed to show an association between respiratory illness before the age of two and gas cooking at home, and acknowledged the literature is inconsistent regarding the health effects of gas stoves.

Harrington et al., unlike the results of their ambient NO_2 exposure trial, did not find an association between gas cooking and respiratory illness.[17] Similarly, Ogston and colleagues did not find an association between gas cooking and hospitalisation or illness experienced in the first year of life.[29]

The numbers of children involved in these studies were large and ranged from 630 to 10106. These sample sizes should have provided adequate statistical power to detect small or modest increases in respiratory illness associated with exposure. The lack of positive findings in some studies may be partly due to bias in illness reporting, especially in those studies that used cross-sectional designs. Recall bias may have occurred with the use of retrospective questionnaires, in that parents of symptomatic children may have preferentially recalled childhood illnesses. Also, varying definitions of illness between studies may have led to the inaccurate recording of illness in some studies. Standardised questionnaires were not used in all studies. These sources of bias may have contributed to the inconsistent findings.

A number of authors[5,25,30] consider the mixed results may in part be explained by misclassification of subjects, favouring a reduction in the magnitude of an observed association between exposure and effect, leading to the absence of a demonstrable association between exposure and illness in some studies.[5] The lack of knowledge about an individual's true exposure to NO_2 is thought to cause this misclassification, since the presence of gas cooking in the home does not necessarily mean a high level of personal exposure. This is highlighted in a number of studies.

Spengler and co-workers measured NO_2 levels inside and outside 137 homes in Portage, Wisconsin, over a one year period. Palmes diffusion monitors were repeatedly used to measure NO_2 levels over one week intervals in homes with gas and electric stoves. Monitors were placed in the kitchen, the bedroom of a child and outside the house. Twenty-five homes had electric stoves, 36 natural gas and 76 liquid propane stoves. Outdoor concentrations were very low and NO_2 levels inside electric-cooking homes were lower than outdoor levels. Levels inside gas-cooking homes were much higher than ambient levels, but levels varied by room. Bedroom levels were found to be 50 to 80% of the kitchen levels in gas-cooking homes. As well, there were strong seasonal effects on the levels of indoor NO_2. This study showed very large variation in the long-term averages for NO_2 among gas-cooking homes. The authors state that "This among-home variation did not allow development of a good regression model for predicting indoor NO_2 concentrations from knowledge of ambient NO_2 levels and type of cooking fuel in the home." They suggested that the large variation would be likely to weaken the association between indoor pollutant exposure and health effects.[31]

Marbury and colleagues investigated indoor residential NO_2 concentrations in 144 homes in Albuquerque, New Mexico. This was in preparation for a study into the relationship between NO_2 exposure and respiratory infections in infants. The activity room and the infant's bedroom in each home were monitored with Palmes diffusion tubes for two two-week cycles during November and December 1994. Ambient levels were recorded at the same time. Outdoor concentrations exceeded indoor concentrations in electric-stove homes, while indoor concentrations exceeded those outdoors in homes with gas stoves. This was consistent with Spengler's findings described above. There was wide variation in NO_2 concentrations (7 - 168.7 ppb) in homes with gas stoves. The concentrations in twenty percent of these homes were in the same range as homes with electric stoves. As well, the levels were significantly

higher in the activity room that the infant's bedroom. The levels in these two rooms were the same in electric-stove homes. A number of household characteristics, such as the presence of a toaster, microwave, wall or floor gas furnace, also influenced the indoor NO_2 concentrations recorded. Analysis revealed that a prediction model for indoor NO_2 exposure, based on these results, is possible, which is an improvement over the dichotomous classification system based on stove type. However, the authors make the point that even a prediction model is no substitute for direct measurement.[32]

These studies demonstrated wide variation in NO_2 concentrations in homes with gas stoves, many with levels equal to those in homes with electric stoves. This may partly explain the lack of consistency in the research findings. This lack of consistency does not allow a definitive statement to be made about the health risks posed by NO_2 produced by gas cooking at home.

Indoor nitrogen dioxide monitoring studies

Mixed results have also occurred in the few studies that measured indoor NO_2 levels and attempted to estimate personal levels of exposure (Table 2.4).

Florey et al., as they did with gas cooking, found a positive association with NO_2 levels that increased with higher bedroom levels.[21]

Houthuijs and co-workers, in the study previously reported, also found a positive relationship with estimated personal exposure levels of NO_2.[25]

Berwick and colleagues, using a prospective design, found an increase in lower respiratory symptoms in children aged less than seven exposed to greater than 0.015 parts per million (ppm) of NO_2.[30]

Neas et al., using Palmes diffusion tubes to estimate mean annual household NO_2 levels, found that a 15 parts per billion (ppb) increase in the

mean exposure level was associated with an increased cumulative incidence of lower respiratory symptoms.[33]

Five studies, however, failed to demonstrate a positive relationship (Table 2.4). Melia and researchers[34] detected no significant relationship between average measured NO_2 levels in bedrooms and living rooms and respiratory illness. This result was contrary to their original findings[19,20] using gas cooking as a measure of exposure. They discounted high humidity or low temperature as being responsible for the discrepancy.

Hoek et al. used Palmes diffusion tube measurements and activity data to determine personal levels of exposure in a case-control study. Cases and controls were selected from data gathered by the School Health Service. Cases were defined by a history of bronchitis, asthma, frequent cough or colds and allergy. The authors point out that bias may have been present due to the high mobility of the study population, and that attempts to estimate historical exposure were inaccurate. No relationship between NO_2 and respiratory illness was found.[35]

Koo and co-workers used passive diffusion badge monitors worn for twenty-four hours to measure personal NO_2 levels of exposure. They reported these monitors as having an accuracy of plus or minus twenty percent when compared to other recognised forms of monitoring. Monitoring was conducted during one week for each subject and no association was found between the children's NO_2 exposure levels and respiratory symptoms.[36]

Dijkstra and colleagues estimated weekly average NO_2 concentrations at home using Palmes diffusion tubes and used these as a measure of level of exposure. No association between NO_2 home exposure and respiratory symptoms was found.[37]

Samet et al. serially measured NO_2 concentrations in bedrooms of 1205 children in their first 18 months of life. Monitoring involved the exposure of Palmes tubes for two weeks. Misclassification of the exposure of subjects was unlikely. Daily diaries were used to record respiratory symptoms, and upper and lower respiratory tract episodes were defined. No association was found between NO_2 levels of exposure and illness incidence or duration.[38]

The number of subjects included in the studies by Melia[34], Hoek[35] and Koo[36] and their co-workers were small. These studies may have lacked adequate statistical power or the ability to detect small or moderate differences in respiratory illnesses between exposure groups. As well, these three studies and that by Dijkstra[37] used cross-sectional designs and different retrospective questionnaires to determine health data. As mentioned previously, this may have involved bias in illness reporting that may have contributed to the mixed results.

Different methods of determining personal levels of exposure make comparisons between these studies difficult. For example, Florey[21], Berwick[30] and Melia[34] carried out home monitoring only, while Houthuijs[25] and Hoek[35] combined home monitoring with time activity data in an attempt to estimate personal exposure. Koo, on the other hand, used monitors worn by subjects over twenty four hour periods to determine levels of exposure.[36] While atmospheric measurements in these studies are likely to be accurate, measurement errors in relation to levels of personal exposure may have occurred in some studies. In the absence of personal monitoring, known activity of children should be considered along with atmospheric measurements to more accurately reflect personal levels of exposure.

Table 2.4 Studies that undertook objective measures of indoor nitrogen dioxide levels

Design	Mean NO_2 levels	Symptom measure	Results	Reference
Cross-sectional N=808 children aged 6-11yrs	0.018 ppm to 0.122 ppm; diffusion sampling in kitchens and 25% bedrooms	Symptoms based on Medical Research Council Ques. (MRCQ)	Positive association that increased with higher NO_2 bedroom levels.	Florey et al. 1979 (21)
Cross-sectional N=630 children aged 6-9yrs	Palmes tube and time budgeting for personal exposure: 0.013 ppm	World Health Organization Ques. for respiratory symptoms (WHOQ)	Personal exposure was associated with higher symptom prevalence.	Houthuijs et al. 1987 (25)
Longitudinal N=121 children aged less than 7 yrs	Passive diffusion monitoring; 6-90 $\mu g/m^3$ 0.003-0.045 ppm	Bi-weekly phone calls for symptoms and lower resp. illness (LRI)	Increased LRI risk in children exposed to 30 $\mu g/m^3$ (0.015 ppm)	Berwick et al. 1987 (30)
Cross-sectional N=1567 children aged 7-11yrs	Palmes tubes for 2 weeks to estimate mean annual NO_2 home exposure	ATSQ given on three separate occasion for respiratory symptoms	15 ppb(billion) ↑ in NO_2 annual household mean assoc. with ↑ cumulative incidence of LRI	Neas et al. 1991 (33)
Cross-sectional N=179 children aged 5-6yrs	Passive diffusion monitors; 0.005 to 0.161 ppm in bedrooms; 0.009 to 0.292 ppm in living rooms	Questionnaire for respiratory symptoms and illness	No significant association found between average NO_2 levels and respiratory conditions	Melia et al. 1982 (34)
Case-control N=231 children aged 6	Palmes tubes and activity data; 44 to 114 $\mu g/m^3$; 0.02 to 0.057 ppm	Questionnaire for symptom and illness occurrence	No difference occurred indoors between cases and controls.	Hoek et al. 1984 (35)
Cross-sectional N=362 children aged 7-13yrs	Passive diffusion badges; Mean levels 13.03 to 23.11 ppb	MRCQ and ATSQ used for illness and symptoms	No association between children's NO_2 exposure level and respiratory symptoms	Koo et al. 1990 (36)

Table 2.4 Studies that undertook objective measures of indoor nitrogen dioxide levels (cont.)

Design	Mean NO_2 levels	Symptom measure	Results	Reference
Longitudinal and cross-sectional N=1051 children aged 6-12yrs	Weekly Palmes tubes; Average exposure 20-60 $\mu g/ m^3$	Modified WHOQ for respiratory symptoms	No association between NO_2 home exposure and reported respiratory symptoms	Dijkstra et al. 1990 (37)
Longitudinal N=1205 children from birth to 18 months	Palmes tubes for 2 weeks in bedroom; 78% of time at risk by bedroom $NO_2 \leq$ 20 ppb	Daily diaries by mothers: biweekly phone calls; nurse home visits	Incidence and duration of respiratory illness was not associated with NO_2 exposure	Samet et. al. 1993 (38)

METHODOLOGICAL CONSIDERATIONS

There are a number of issues that arise out of these studies. Those that used ambient air monitoring or the presence of gas cooking to classify NO_2 exposure have not provided an understanding of the association of levels of exposure with adverse health effects. Those studies, in which objective indoor measurements were made, used different methods of exposure estimation and produced mixed results.

As well, most studies used cross-sectional designs with retrospective, parental questionnaires to record information about children's health. These questionnaires are subject to bias introduced by the state of the child at the time of the questionnaire[5,22] and the parents' lack of knowledge of events that might have occurred over previous years.[22]

Confounding, the effect of other variables that may be associated with exposure and risk for an outcome, also needs to be considered. Confounders may cause an overestimate, underestimate, or may even change the direction of a true association between exposure and disease.[39] Control of potential

confounders, including smoking, asthma, and socio-economic status, has been variable in the reported studies.[5]

It is possible that unpublished studies with negative findings may exist. For the reasons already mentioned, negative findings from studies that used gas stoves as surrogate measures of exposure would be of limited value. However, negative findings from studies that objectively quantified dose may be important. Pooling of results, including those from unpublished studies, could help to overcome the effects of inadequate power in some studies with small sample sizes.

The issues raised make interpretation of the conflicting results difficult and do not provide adequate evidence from which to set a maximum hourly or twenty-four hourly average indoor goal for NO_2.[11]

ANIMAL TOXICITY AND NO_2 EXPOSURE PATTERNS

Animal studies have provided some understanding of the toxicity associated with different patterns of NO_2 exposure by measuring mortality rates after bacterial exposure. Gardner et al. point out that this infectivity "model probably best reflects a summation of all the possible responses to the pollutant assault on the lung, such as edema, inflammation and subtle immunological and cellular alterations."[40]

Gardner and colleagues examined the dose-time response in mice, exposed to six concentrations of NO_2 (0.5, 1.5, 3.5, 7.0, 14.0, and 28.0 ppm) for varying periods of time up to twelve months, prior to challenge with streptococcus pyogenes. Results showed that mortality increased with increasing duration of exposure to any given concentration and also increased with increasing concentration of exposure. The authors also compared two different concentrations of NO_2, where the exposure time was adjusted to keep

the concentration multiplied by time (concentration × time) factor constant. They found the mortality rate was approximately five times higher at 14 ppm than at 1.5 ppm. This result suggests that the concentration of exposure may be more important than the duration of total dose of exposure in producing a toxic effect.[41]

The same authors also examined the effect of either intermittent or continuous exposure to 1.5 ppm or 3.5 ppm in mice followed by similar bacterial exposure. Mice were intermittently exposed for 7 hours per day, 7 days per week for periods up to 20 days. At various times, their mortality was compared to mice exposed continuously for the same period. For any given length of total exposure, there was no statistically significant difference between the mortality in the two groups. This suggested that intermittent exposure may be as toxic as continuous exposure. The authors point out that "These data indicate the importance that short-term peaks may have upon responses to environmental pollutants."[40]

Gardner[42], Graham[43] and their co-workers examined the effect of spike exposures to NO_2, with and without a background of continuous low level exposure. Mice were exposed to spike levels of 4.5 ppm for up to seven hours followed by bacterial exposure. When challenged by streptococcus immediately post exposure, mortality was proportional to the duration of the spike. This susceptibility disappeared eighteen hours after exposure ended. Recovery from the NO_2 "assault" was offered as the probable reason for this result. This recovery, it was suggested, "may have been facilitated either by direct repair of specific damages or the influx of additional host defences, such as the influx of alveolar macrophages or polymorphonuclear leckocytes, which may have some capabilities to protect the lungs against the subsequent invading organisms."[42] However, when the same spikes were superimposed on a background of continuous exposure to 1.5 ppm, the recovery after eighteen hours

disappeared. Inability to recover or inability of influxing cells to function were offered as possible explanations for this effect.[42] This may be relevant to human situations, where spikes occur on a background of continuous NO_2 exposure. Against a background of continuous exposure, spike induced changes to human lung defences may persist, leading to increased susceptibility to respiratory infection. Mice were also exposed to two daily one-hour spikes of 4.5 ppm NO_2 over two weeks superimposed on a continuous background of 1.5 ppm. Mortality was compared with that for continuous exposure to 1.5 ppm only. The mortality in mice exposed to spikes was equivalent to that of mice exposed to 1.5 ppm continuously for that period. This again highlights the complexity of the relationship between spike exposure and toxicity.

Miller and colleagues conducted a similar study using spike concentrations. Mice were exposed to a continuous baseline of 0.2 ppm NO2 upon which were superimposed two 1-hour spikes of 0.8 ppm 5 days per week. Mortality was compared with mortality in control mice, or mice that received only baseline exposure to determine the contribution of the spikes to toxicity. The study chose a ratio of 4:1, spike to background level, based on data from the EPA's Storage and Retrieval of Aerometric data (data base) which indicated spike to base ratios of 3:1, 4:1 and 5:1 are not uncommon in the urban environment. The infectivity mortality of mice in the spiked exposure regimen was significantly greater than that in either the NO2 background exposed mice or the control mice. The authors made the point that "the body of information from NO2 infectivity studies in mice now even more clearly indicate the peaks of exposure are the determinants of effects on lung antibacterial defences. Thus, it may be hypothesized that the risk to humans exposed to NO2 is also dependent on the pattern of exposure, especially the pattern of spikes."[44]

In summary, these results showed that concentration was associated with greater susceptibility to infection than duration of exposure, and that short term spikes were associated with increased toxicity. These studies involved spike to background ratios of 3:1 or 4:1 ppm of NO2. The significance of these studies in relation to humans will be further discussed later in this chapter.

INFECTIVITY AND HOST DEFENCES

Animal studies have clearly demonstrated an association between NO_2 levels of exposure and the increased frequency of experimentally induced respiratory infection. As well, exposure to intermittent spikes of NO_2 increased severity. Associated effects on the host defence mechanisms of animals have also been demonstrated. These include impairment of mucociliary clearance and reduction in the number of viable macrophages.[45] Frampton and colleagues[46] suggest that impaired killing of bacteria in the lung is the mechanism by which the host defence mechanism is defective. However, little is known about the relationships between NO_2 levels of exposure, lung defence mechanisms and respiratory tract infections in humans.

Goings and co-workers attempted to address this issue by investigating the effects of NO_2 exposure on the susceptibility of human adults to an influenza virus. This involved double-blind randomised, placebo controlled trials conducted over 3 separate years. Each year, healthy non-smoking adults were exposed to clean air or NO_2 for 3 days. Different protocols involving 1, 2 and 3 ppm were used. Subjects were required to complete a respiratory symptom questionnaire each day. At the end of the second day of exposure, each subject was inoculated intranasally with influenza A vaccine virus. Although not statistically higher, rates of infection were increased in some of the NO_2 groups. The authors concluded that NO_2 may increase adult susceptibility to respiratory virus infections.[47] Frampton et al., however, point out that "the virus used in this study was incapable of infecting the lower

respiratory tract. Thus possible alterations in defence mechanisms at the alveolar level, which has particular relevance for NO_2 exposure, were not tested.[46]

Frampton and colleagues investigated the effects of NO_2 inhalation in vivo on the ability of human alveolar macrophages to inactivate influenza virus in vitro. An environmental chamber was used to expose normal volunteers sequentially to air or NO_2, using double-blind randomisation. Two 3 hour protocols were employed: 9 subjects were exposed to a continuous level of 0.60 ppm, while 15 subjects received three 15 minute peaks of 2.0 ppm of NO_2 on a continuous background of 0.05 ppm. "Alveolar macrophages obtained by bronchoalveolar lavage three and a half hours after exposure to continuous 0.60 ppm NO_2 tended to inactivate influenza virus in vitro less effectively than cells collected after air exposure."[48] These findings suggest low level exposure to NO_2 may induce subtle changes in mechanisms of cellular host defence at the alveolar level.[46] Samet and Utell suggest the method used in this study provides a technique to study the effects of pollutant exposure on the defence mechanisms of the lower respiratory tract.[49]

Exposure to NO_2 has therefore been linked to impaired host defence mechanisms in both humans and animals. Gardner points out that the animal model can be used to reflect the toxicological response in humans but that the appropriate endpoint for comparison in humans should be the increased prevalence of community respiratory illness. "Such a comparison is proper since both mortality (animal) and morbidity (humans) result from a loss in pulmonary defences."[45]

CONTROLLED HUMAN EXPOSURE STUDIES

Controlled human exposure studies have provided information about low-level NO_2 exposure and adverse health effects. Many studies have been

undertaken (Table 2.5), involving the exposure of voluntary subjects to known concentrations of one or more pollutants and the recording of associated pulmonary changes, including respiratory symptomatology, spirometric lung function, bronchial reactivity and airways resistance. Advantages of such studies include the ability selectively to recruit specific types of individuals, the knowledge of the nature, duration and level of exposure, and the opportunity to study pulmonary responses in detail.[4] The major disadvantage is that subjects are exposed for only a short time under experimental conditions that do not necessarily reflect outcomes that would be obtained with chronic low level exposure in normal environments. While some experiments have included intermittent exercise that may affect dose, this does not reflect changes in dose experienced by individuals due to movement between environments with differing concentrations. As well, chamber studies do not necessarily provide exposure to co-pollutants likely to be present in normal environments. In the studies reported, subjects with normal respiratory systems, asthma and chronic obstructive lung disease were exposed to levels of NO_2 that ranged from 0.1ppm to 5 ppm. Exposure times varied from ten minutes to four hours, with or without concurrent exercise.

A positive association between NO_2 levels of exposure and respiratory symptoms was found in only one[50] of many studies.[50-58] Linn and colleagues found a significant increase in respiratory symptoms in normal subjects immediately post exposure, and in asthmatics later in the day, after exposure to 0.5 ppm.[50] However, sulphur dioxide was included in the exposure mixture, making it impossible to determine the contribution of nitrogen dioxide to symptom production. Kleinman and co-workers found significantly fewer symptoms in asthmatic than control subjects exposed to 0.2 ppm of NO_2 for two hours with intermittent exercise.[52] The authors claimed this implausible finding was most likely due to a chance effect.

Table 2.5 Controlled human exposure studies

Design	NO_2 conc.	Exposure time	Results	Reference
Uncontrolled 5 normal adult males	4 to 5 ppm	10 minutes: seated	No change in spirometric readings following exposure	Abe 1967 (66)
Uncontrolled 55 healthy male adults 84 males with chronic bronchitis	5 ppm	15 to 100 minutes	Dose dependent increased airways resistance above 1.5ppm NO_2	von Nieding et. al. 1973 (59)
Randomised, single blind controlled: 13 male and 7 female asthmatics aged 15 to 44 years	0.1 ppm 0.2 ppm	1 hour	Increased airways resistance and bronchial reactivity in 13 of 20 subjects at 0.1ppm NO_2	Orehek et. al. 1976 (62)
Randomised controlled 15 healthy adult males	0.6 ppm	2 hours: exercise	No pulmonary function changes were seen	Folinsbee et. al. 1978 (67)
Single blind controlled 20 normal adult males	1.0 ppm	2 hours: intermittent exercise	Non-significant increase in symptoms of the exposed over the control group	Hackney et. al. 1978 (51)
Controlled 11 healthy adult males	5 ppm	2 hours: intermittent exercise	Increased airways resistance after NO_2 exposure	von Nieding et. al. 1979 (60)
Controlled 20 normal and 19 Asthmatic adults	0.5 ppm	2 hours: intermittent exercise	Significant increase in symptoms in normals post exposure and asthmatics later in the day. No changes in lung function	Linn et. al. 1980 (50)
Randomised double blind controlled: 6 asthmatic subjects	0.1, 0.3 0.5 and 1.0 ppm	4 hours	Pulmonary function was unchanged	Sackner et. al. 1981 (68)
Single blind cross-over controlled 20 normal and 20 asthmatic subjects	0.1 ppm	1 hour	No change in baseline airways function . A variable effect on bronchial reactivity was seen in both groups	Ahmed et. al. 1982 (64)
Purified air controlled 31 asthmatic subjects	0.2 ppm	2 hours: intermittent exercise	Sig. less symptoms in the NO_2 exposed group. Airways resistance was not increased	Kleinman et. al. 1983 (52)
Randomised double blind controlled: 15 normal and 15 asthmatic subjects	0.1 ppm	1 hour: resting	No demonstrable airways effects in either group	Hazucha et. al. 1983 (63)
Single blind cross-over controlled: 10 asthmatic adults	0.3 ppm	30 minutes: light exercise	NO_2 potentiated exercise induced bronchospasm and airways reactivity after cold air provocation	Bauer et. al. 1984 (69)

Table 2.5 Controlled human exposure studies (cont.)

Design	NO_2 conc.	Exposure time	Results	Reference
Double blind controlled 10 healthy and 10 asthmatic adolescents	0.12 ppm	1 hour resting	No consistent significant lung function changes were found	Koenig et. al. 1985 (65)
Controlled 12 asthmatic subjects	0.3 ppm	110 minutes: exercise	NO_2 caused significant decrements in pulmonary function testing	Roger et. al. 1985 (71)
Controlled 8 normal and 8 asthmatic subjects	0.12 to 0.48 ppm	20 minutes	Increased bronchial reactivity in asthmatics. Significant increase in airways resistance in normals	Bylin et. al. 1985 (61)
Controlled 25 normal and 23 asthmatic subjects	4 ppm	75 minutes: exercise	No significant effects on symptomatology or lung function were found	Linn et. al. 1985 (53)
Controlled 22 adults with COAD	0.5, 1.0, 2 ppm	1 hour: exercise	No significant symptom or lung function effects were found	Linn et. al. 1985 (54)
Controlled 21 asthmatic subjects	0.3, 1.0, 3.0 ppm	1 hour: moderate exercise	No significant symptom or spirometric lung function changes. Airways resist. increased with NO_2 exposure	Linn et. al. 1986 (55)
Controlled 15 asthmatic subjects	0.3 ppm	30 minutes: exercise	NO_2 potentiated exercise induced bronchospasm and airways reactivity after cold air provocation in asthmatics	Bauer et. al. 1986 (70)
Double blind randomised controlled: 10 asthmatic subjects	0.5 ppm	1 hour: resting	No significant increase in symptoms or lung function after exposure. Airways reactivity was significantly increased post exposure	Mohsenin 1987 (56)
Double blind randomised controlled: 18 normal adults	2.0 ppm	1 hour: resting	No significant increase in symptoms or lung function after exposure. Airways reactivity was significantly increased post exposure	Mohsenin 1987 (57)
Double blind cross-over controlled: 40 normal, 20 asthmatic and 20 COAD subjects	0.3 ppm	225 minutes: exercise	No significant symptom effects in any group. Impaired lung function testing in COAD	Morrow & Utell 1989 (58)
Double blind randomised controlled: 39 subjects in three groups with different exposure protocols	0.6 ppm 0.05 + peaks of 2 ppm: 1.5 ppm	3 hours: exercise	1.5 ppm continuous NO_2 for 3 hours increased bronchial activity in normal subjects	Frampton et. al. 1991 (72)

Increased airways resistance following NO_2 exposure has been found in normal and asthmatic subjects at concentrations at or above 0.3 ppm.[55,59-61] At lower concentrations, Orehek and co-workers[62] found an increase in airways resistance in thirteen out of twenty asthmatic subjects at 0.1 ppm, while Kleinman et. al.[52] and Hazucha and colleagues[63] found no such increase at or below 0.2 ppm.

Although baseline lung function remained unchanged in many studies involving exposure levels ranging from 0.1 ppm to 5 ppm,[50,53-55,63-68] Bauer and colleagues[69,70] and Roger et. al.[71] independently demonstrated that NO_2 potentiated exercise induced bronchospasm in asthmatic subjects at 0.3 ppm.

Finally, increased bronchial reactivity has been demonstrated at or above 0.3 ppm in a number of studies.[56,57,61,69,70,72] While Orehek et al.[62] found a similar increase in airways resistance at 0.1 ppm, Abramson[4] points out that inappropriate statistical techniques were used in their analysis.

The contribution of this association of 0.3 ppm NO_2 with increased airways resistance, exercise induced bronchospasm and increased bronchial reactivity to the air quality guidelines set by the World Health Organization (WHO) and the National Health and Medical Research Council (NHMRC) will be discussed later in this chapter.

THE AUSTRALIAN EXPERIENCE

The State Pollution Control Commission (SPCC) of New South Wales (NSW), in determining air quality for urban air pollutants, adopted the NHMRC's ambient NO_2 guideline of 0.16 ppm (1 hour maximum) as the level of concern.[73] In 1988, the Commission reported that the ambient NO_2 level exceeded this one hour goal on no more than seven days in that year in their monitored areas. This tends to indicate that outdoor NO_2 exposure is likely to

be small and this is supported by the ambient studies reported previously (Table 2.1).

In the same year, the first Australian study of indoor NO_2 levels was carried out in the Sydney metropolitan area and the adjacent Blue Mountains of NSW. Nitrogen dioxide levels were measured using passive badge monitors in sixty-four homes. Up to fifty-eight percent of homes were found to have levels that exceeded 0.16 ppm.[74] Ferrari and co-workers concluded that an estimated half a million residents were exposed to NO_2 levels that exceeded this goal, and that residents may have experienced such levels up to three hundred times during a winter heating period. They suggested such excesses were likely to occur even more frequently in the colder climates of Tasmania and Canberra.

A later discussion paper described a study of the levels of NO_2 in over six hundred NSW school classrooms heated by flueless gas heaters. The study was commissioned by the Department of Education and co-ordinated by the SPCC with the assistance of the Australian Gas Light Company. Nitrogen dioxide levels ranged from 0.01 ppm to 2.90 ppm, being higher in poorly ventilated, unoccupied classrooms with greater heater use. However, even when directions were issued to schools to ensure adequate ventilation, thirty percent of school rooms still had levels of NO_2 that exceeded 0.16 ppm.[75]

AIR QUALITY GUIDELINES

The WHO recommends goal levels of 0.08 ppm over twenty-four hours and 0.21 ppm over one hour for ambient NO_2 exposure.[9] It has not set a separate goal for indoor exposure. The one hour goal is based on the judgement that the controlled human exposure level of 0.3 ppm is the "lowest-observed-effect-level" found in asthmatic subjects, and that a lower level provides a further margin of safety. The twenty-four hour goal is based on the judgement that repeated exposures approaching this level are to be avoided,

so as to create a margin of safety against chronic effects. The NHMRC accepts that indoors, "NO_2 may cause clinical effects in some individuals above 0.3 ppm hourly average." This recommendation, made at a NHMRC consensus meeting in Canberra in 1990, was also based largely upon the findings of the controlled human exposure studies described earlier. The Australian experience indicates that a significant number of people may be exposed to a greater than 0.3 ppm NO_2 hourly average, especially in school classrooms. The question remains, however, whether or not these guidelines, based on experimental studies, are satisfactory for chronic low-level exposure under normal environmental conditions. Methodological weaknesses, conflicting results and lack of environmental monitoring in the majority of instances have not to date provided the epidemiological evidence necessary to provide an answer.

DISCUSSION

A number of shortcomings have been found in published studies. Those that measured ambient NO_2 levels were unable to separate out the illness effects attributable to NO_2 from those due to other pollutants. The information provided by controlled human exposure studies was limited by very short durations of exposure under artificial conditions, quite unlike the nature of exposure experienced by people in normal environments. A majority of childhood epidemiological studies used gas cooking as a surrogate measure for NO_2 exposure, with misclassification of subjects being a possible explanation for their mixed results. As well, most of these were cross-sectional studies that relied on retrospective data collection.

Few studies objectively measured indoor NO_2 and all but one[36] relied on cumulative measures over weeks to determine exposure classification. While it is important to understand the effects of such cumulative exposures, animal studies indicate that short term spike levels of exposure are equally, if not more

important than cumulative dose in the disease process. Lack of information about spike levels of exposure may have contributed to the inconsistent findings.

This view is supported by the members of the European Communities Concertation Committee in a report on the effects of indoor air pollution on health. The committee states that "Of the combustion products, NO2 has been studied widely in the past decade. Many studies have used proxy measures of exposure rather than actual NO2 measurements by contrasting populations living in homes with unvented gas cooking appliances with populations living in homes equipped with electric cookers. It has been shown that this may lead to sizeable misclassification of exposure to NO2. Some studies have used indoor and personal monitoring of NO2 instead, usually by employing diffusion samplers which require exposure times of several days to a week. As a result, only long-term average exposure levels were available in these studies. Animal experiments have suggested that repeated exposure to peak concentrations may be more harmful to health than exposure to long-term average concentration levels resulting in the same inhaled dose. As peak concentration levels do occur in homes, and as their relationship with long-term average concentration levels is likely to be weak, exposure to NO2 may have been inadequately characterized even in those studies that have employed large-scale passive sampling of NO2 in homes and on persons. It is conceivable that the inconsistency of the results of epidemiological studies conducted so far is partly related to this issue, as peak concentration levels in homes have been shown to exceed the 1987 WHO health guidelines by a fairly large margin in a fairly large proportions of homes."[76]

These issues highlight the reasons why existing studies do not provide a clear understanding of the association between indoor exposure to NO_2 and

respiratory illness. They do not provide adequate epidemiological evidence upon which to set safe goals.

The importance of spike exposures in relation to toxicity have been discussed and their possible importance in relation to epidemiological studies has been suggested. However, the different levels of NO2 involved in animal and epidemiological studies are an important consideration if the animal model is to be used a basis for epidemiological study. As mentioned, NO2 levels in Australian classrooms have been recorded as high as 2.9 ppm. This suggests that some children may be exposed to levels of NO2 of the same order of magnitude as that used in the animal study by Miller.[44] Other animal studies used levels of NO2 that were an order of magnitude higher. Nevertheless, all relied on design ratios of 3:1 or 4:1 spike to continuous levels of NO2 exposure. This raises the issue of the relationship of absolute concentrations of exposure to the pattern of spike to continuous exposure. This relationship is unclear. Since increased mortality has been associated with the spike pattern of exposure over different orders of magnitude of NO2 concentrations in animals, the pattern of exposure, apart from the absolute levels of exposures, appears to be significant. If so, a differential effect in morbidity in humans may occur at lower concentrations involving repeated spikes superimposed on a continuous background. This rationale provided the basis upon which the exposure design methodology was targeted in this study.

With the aid of new technology and a prospective design, a study was proposed that aimed to circumvent the problems identified. The objective of this study was to investigate the association between exposure to spike levels of NO_2 and respiratory illness. Spikes were to be identified as short-term increased levels of NO_2 over background levels occurring indoors. An instrument was needed to measure short term exposures to NO_2. The passive diffusion badge monitor, which was suitable for use with exposure times from

one to twenty-four hours, was selected. These monitors will be described fully in the next chapter. The study was to be based on a selection of school children, a subset of whom were known to be exposed to unflued gas heating during winter. Daily respiratory diaries were chosen to allow prospective symptom data collection. The objective was to compare symptom rates in children based on exposure to spike levels of NO_2. Symptom data were also to be used to characterise illness episodes in children for further comparison. Children were selected as study subjects because of their increased susceptibility.

Prior to the commencement of the main study, however, it was important to ensure that the requirements could successfully be met to use passive diffusion badge monitors in an epidemiological study. These monitors had not previously been used in such a trial in Australia and had only been included in one reported overseas trial.[36] As well, the most cost-efficient monitoring protocol to reflect spike exposure levels had not been determined. A pilot study, the description of which follows, was conducted in 1991 to address these issues.

CHAPTER 3

THE 1991 PILOT STUDY

The 1991 pilot study was carried out in preparation for the main observational study undertaken in 1992. Its main aims were to determine the suitability of the environmental monitoring instrument, to determine the most appropriate environmental monitoring protocol for the study objectives and to ensure that symptom data collection methods were satisfactory. Passive diffusion badge monitors had been used in only one previously reported study, in which children wore monitors for twenty four hours.[36] While this protocol determined daily concentrations, it did not take into account the effects of indoor and outdoor exposure. Long periods of outdoor exposure to low levels of NO_2 were likely to have masked the concentrations experienced by children when exposed to NO_2 during times of gas use. A pilot study was necessary to determine the most appropriate method of measuring NO_2 during times of gas use, which, in turn, would reflect spike daily levels of exposure as described in Chapter 2.

Canberra was chosen as the area in which to conduct the pilot study. Its cold climate was sure to guarantee the use of substantial indoor heating over winter. Also, unflued gas heating was commonly used and was expected to provide people with significant exposure to NO_2. Selection of a school with electric heating and one with unflued gas heating was considered a suitable way of providing a control group and a NO_2 exposed group of children. The Catholic Education Office agreed to provide access to such schools, to permit the voluntary selection of children and to allow air monitoring to be undertaken. Approval for the study was received from The Australian National University's Ethics Committee. Canberra's Public Health Laboratory and the Air Quality Laboratory of the State Pollution Control Commission (SPCC) of New South

Wales agreed to collaborate on the manufacture and analysis of monitoring instruments.

This chapter outlines the sample selection for the pilot study, describes the instruments used, explores different protocols for air monitoring, compares levels of exposure with health effects, and concludes with recommendations for the main study.

METHODOLOGY

Sample selection

With agreement by school Principals, one primary school with electrically heated (control school) and one with unflued gas heated classrooms (exposed school) were selected to participate. One hundred names were provided from each school, which, according to the Principal, constituted almost the entire number of children exposed to unflued gas heating in the exposed school. The hundred children in the control school were selected to match the age distribution of children in the exposed school. Letters were handed out to children to be taken home to their parents inviting them to take part in the study. Eighty three parents from the control school and 48 from the exposed school sent back signed acknowledgments that they agreed to participate. It was decided at that point to limit the overall number of subjects to less than one hundred children in order to conserve resources. This number was sufficient to allow variations in the air monitoring protocol to be assessed and to allow daily respiratory diaries to be trialled. Consequently, respiratory health questionnaires were sent to the parents of the first 50 replies received from the control school and the 48 parents from the exposed school. The final sample was made up of 49 control and 41 exposed children, after exclusion of those whose parents did not return the questionnaire.

Nitrogen dioxide monitoring

In view of the importance of spike exposures noted in Chapter 2, short-term exposure monitoring was preferred. This was a departure from the objective methods of measurement used in previous epidemiological studies that used Palmes tubes to produce cumulative exposure measurements over weeks to classify subjects.

Passive diffusion badge monitors were therefore selected as the instruments of choice for this study (Figure 3.1).

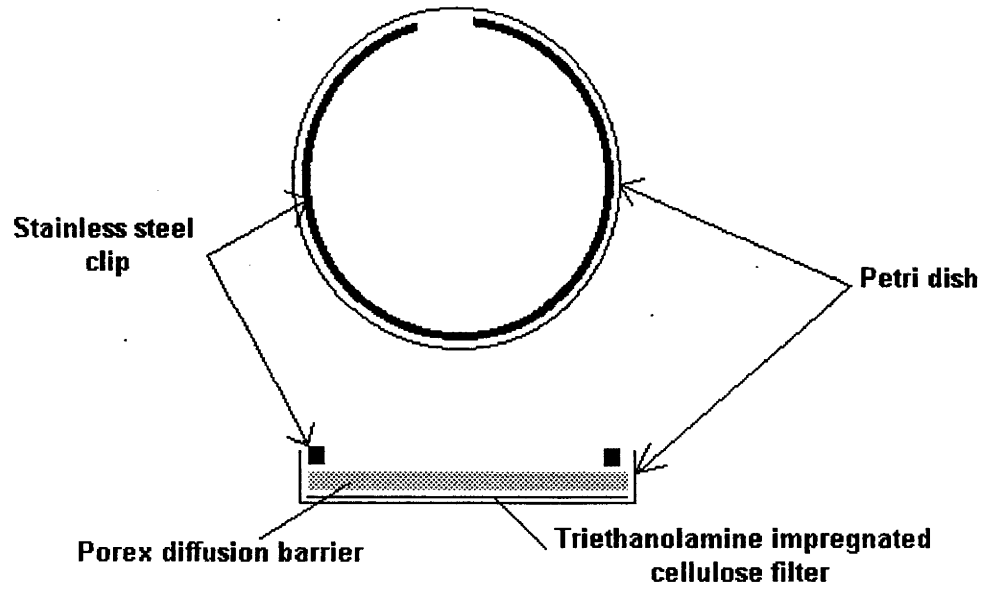


FIGURE 3.1 Passive diffusion badge monitor

Each monitor consisted of a 50mm petri-dish badge case containing a triethanolamine impregnated cellulose filter covered by a porex diffusion barrier held in place by a stainless steel clip. The manufacture of these monitors was consistent with specifications of the Standards Association of Australia.[77] This method is designed to measure indoor air with an expected NO_2 concentration between 0 and 3 ppm for an exposure time of one hour. It has a detection limit

of 0.035 ppm for a two hour sampling period and has been shown in test atmospheres to have an accuracy within ten percent of chemiluminescence analysers.[69] The size, accuracy and portability of these monitors made them ideal for the repeated, large scale, short-term monitoring protocol planned for this project.

The monitors were manufactured at the SPCC by staff of the Air Quality Laboratory who had been involved in the development of the Australian Standard. Each monitor had its own protective cover plate and was stored in a protective plastic bag containing a capture badge to absorb any unwanted NO_2 that might have entered the bag. Batches of badge monitors were assembled and couriered from the SPCC to Canberra and taken to the respective schools on the first day of each monitoring period.

In all, monitoring was conducted on 44 children from the control and 35 children from the exposed schools. Eleven children were not included due to a lack of available monitors. In two separate weeks in either June or July, 24 children from the control school and 15 from the exposed school wore badge monitors for twenty-four hours over four consecutive days. The remaining 20 children from each school wore a different badge monitor during school time and non-school time, over four consecutive days, in either August or September (Table 3.1). This meant their monitors were exposed for six hours during the school day and for eighteen hours out of school hours.

Table 3.1 Badge monitoring timetable

Date of exposure	Number monitored in the control school	Number monitored in the exposed school
24/6/91 - 27/6/91	8	8
15/7/91 - 18/7/91	16	7
19/8/91 - 22/8/91	10	10
23/9/91 - 26/9/91	10	10

This change to composite school-time and non-school-time monitoring was made to better reflect the spike levels of NO_2 that occurred during the twenty-four hours of exposure, especially during school time.

On each day of monitoring, new badges were taken from their protective bag and, with the cover plate removed, were pinned to the outer front of the child's clothing with the open face of the badge exposed to the atmosphere. They were applied at approximately 9 am each morning and collected at the same time the following morning. For those children for whom composite monitoring was undertaken, the badges were changed at approximately 3 pm. At bedtime, monitors were unpinned and placed on a table near the head end of the child's bed. Following collection, cover plates were reapplied and monitors replaced and sealed in their protective plastic bags. Blanks were included with each batch to allow a correction to be made, during analysis, for any unwanted NO_2 that may have entered the bags during the periods of transportation and storage.

Batches were collected from the schools at the end of each of the four weeks and taken to the Public Health Laboratory for analysis. The technician who undertook the analysis had received appropriate training in Canberra by a member of the SPCC's Air Quality Laboratory. Analysis was conducted in accordance with the procedures set down by the Standards Association of Australia.[77]

Past history and symptom data collection

A respiratory health questionnaire, based on the American Thoracic Society Questionnaire, Division of Lung Diseases[78] with modifications for Australian conditions, was sent to each parent for completion at the beginning of the study period. This questionnaire provided information about the past

health of children, the type of cooking and heating appliances used and whether or not anyone smoked regularly in the home.

Daily respiratory diaries, which have been used effectively and efficiently in previous health studies,[79,80] were employed to collect symptom data. These diaries allowed prospective data collection, and therefore reduced the potential recall bias inherent in the large number of cross-sectional studies undertaken to date.

A set of instructions were sent to parents along with five predated diaries in May 1991. Each diary was designed for the collection of pre-determined symptom data by parents over one month. Symptoms recorded daily were sneezing, stopped up nose, runny nose, sore throat, hoarse voice, dry cough, cough with phlegm, and wheezing. As well, each parent recorded, on a daily basis, if their child had a cold or was absent from school. Completed diaries were returned in reply-paid envelopes at the end of each month from June to October 1991. A "rate" for each symptom for each child was determined by expressing symptom days as a proportion of the number of recorded days of observation.

Analysis of nitrogen dioxide and symptom data

The generation of results occurred in three parts. Firstly, NO_2 levels recorded on badge monitors worn by children from the control and exposed schools were compared using the two-tailed Student's t-test. From this comparison, the most appropriate field monitoring protocol for the main study was determined. In the results that follow, the badge concentration refers to the total amount of NO_2 absorbed onto the triethanolamine filter paper over the period of badge exposure. To determine this concentration, the Australian Standard Spectrophotometric Method was used.[77] Firstly, the absorbances corresponding to increasing concentrations of a solution containing a standard

dye solution were measured, and a calibration graph of absorbance versus concentration was prepared. This was a straight line graph, from which the slope and constant were determined. Then the corrected absorbance (corrabs) for each badge monitor was calculated. This was equal to the absorbance found on each badge monitor minus the absorbance found on its associated blank monitor. The badge concentration (bdgconc) was then determined from the calibration graph according to the formula:

$$\text{bdgconc} = \text{slope} \times \text{corrabs} + \text{constant.} \qquad \text{(Equation 3.1)}$$

The average atmospheric concentration for each badge, on the other hand, refers to a time weighted value generated mathematically from the badge concentration according to the formula:

$$c = k \times \text{bdgconc} \times T \times p_1 \div (T_1 \times p \times t) \qquad \text{(Equation 3.2)}$$

where

c = average atmospheric concentration, in parts per million

k = calibration constant

T = estimated temperature at the sampling site, in kelvins

p_1 = estimated atmospheric pressure during the calibration period, in kilopascals

T_1 = estimated temperature during the calibration procedure, in kelvins

p = estimated atmospheric pressure during the sampling period, in kilopascals

t = exposure time, in hours.

This concentration represents the average concentration of NO_2 in the air experienced over the period of badge exposure. By convention in Australia, NO_2 concentration is reported in parts per million (ppm).

Secondly, the levels found were examined to assess the exposure status of each child. Before any comparison of health data could be made, it was necessary to determine criteria for classification of children into control and

exposed categories. This was not straightforward because of the two different protocols used for air monitoring. Smoking at home was considered to be a criterion for exclusion.

Finally, the mean symptom "rates" between control and exposed children were compared using the Student's two-tailed t-test. To take account of the skewed distribution of scores[81] and of children who did not experience a particular symptom, the natural logarithm of the symptom "rate" plus one was taken as the unit of comparison.

RESULTS

June-July monitoring period

The mean twenty-four hour badge and average atmospheric NO_2 concentrations for the 15 children from the exposed school were statistically significantly higher than those for the 24 children from the control school (Appendix 1 and Table 3.2).

Table 3.2 Mean and standard error for the 24 hour badge and average atmospheric concentrations (ppm) for the children from the control and exposed schools.

	Electrically heated school (n=24)	Unflued gas heated school (n=15)	p value
Mean 24 hour badge concentration	0.151 ± 0.012	0.615 ± 0.085	< 0.001
Mean 24 hour average atmospheric concentration	0.004 ± 0.000	0.015 ± 0.002	< 0.001

These results raised a number of issues for consideration. Although the nitrogen dioxide levels were measurably higher in badges worn by children from the exposed school, the average twenty-four hour atmospheric concentrations of both groups were low when compared to current standards. This did not mean that high levels were not experienced at some time during

the exposure period. The low levels may be explained by the dilution effect of long periods of badge exposure at times of non-gas exposure. These measurements, then, did not reflect short term spike concentrations of NO_2 likely to have been experienced by some children. Also, the protocol did not allow the contributions of NO_2 from schools and homes to be determined separately. This information was important to ensure correct classification of exposure. This led to the decision to undertake separate school-time and non-school-time measurements.

August-September monitoring period

The mean school-time and non-school-time badge and average atmospheric NO_2 concentrations for the 40 children who wore separate monitors during those periods is shown in Appendix 2. The mean school-time concentrations recorded in the unflued gas heated school were statistically significantly higher than those recorded in the electrically heated school (Table 3.3). Comparison of tables 3.2 and 3.3 indicated that about two-thirds of the levels absorbed by badges, which had been placed in unflued gas heated classrooms over twenty-four hours, were likely to have occurred during school-time exposure. Coupled with the shorter (6-hour) duration of badge exposure, the school-time average atmospheric concentrations recorded in the unflued gas school were on average three times higher than those recorded previously in the same school using twenty-four hour monitors. This was due to atmospheric concentration being inversely proportional to the time of badge exposure (Equation 3.2). School only monitoring was a better representation of the daily spike levels experienced within the classroom, bearing in mind that these monitors were worn outside the classroom during recess and lunch breaks.

Table 3.3 Mean and standard error for school-time badge and average atmospheric concentrations (ppm) for the children from the control and exposed schools.

	Electrically heated school (n=20)	Unflued gas heated school (n=20)	p value
Mean school-time badge concentration	0.048 ± 0.005	0.403 ± 0.019	< 0.001
Mean school-time average atmospheric concentration	0.005 ± 0.001	0.044 ± 0.002	< 0.001

To assess the effects of home gas exposure, non-school-time average atmospheric concentrations were examined. Unflued gas appliances were present in only four of the homes that were monitored. The non-school-time average atmospheric concentrations found in these four homes were similar to those found in non-gas appliance homes (Appendix 2). As occurred with the twenty four hour exposure protocol, this eighteen hour protocol did not reflect the short term high concentrations of NO_2 that might have been experienced by children during times of gas use in the four homes concerned. To reflect these concentrations, the exposure periods of home monitors would need to have been restricted, to coincide with times of gas utilisation.

A determination was also made of the variation between monitors worn by children on the same day in the same classroom. This was to explore the possibility of using static monitors in classrooms to record levels of exposure. While personal monitoring is likely to have less random error and is biologically more appropriate, it is logistically more difficult. The use of static monitors would help to reduce some of the logistic difficulties. This approach would allow tighter control of monitors by field workers, would overcome dilution effects of recess and lunch breaks, and would reduce the total number of monitors required. To ensure adequate numbers were included for comparison, only those rooms in which three or more children wore monitors were selected. This resulted in the inclusion of three classrooms from the electrically heated and two from the unflued gas heated schools. The mean of the daily standard

deviations of the school-time average atmospheric concentrations for the electrically heated school was 0.004 ppm. The mean for the unflued gas heated school was 0.013 ppm. The monitors used, which had a limit of detection of 0.035 ppm for two hours, had been exposed for six hours. Therefore, differences between monitor levels of the order of 0.012 ppm or less could be considered to be equivalent. On this basis, the levels recorded by monitors in the same classroom on the same day could be considered equivalent. As a result, static monitors placed in the same classroom on the same day are likely to accurately reflect the classroom level of exposure.

Conclusions on monitoring

The placement of stationary monitors inside classrooms was determined as the most appropriate method to assess school-time levels of exposure. The pilot study showed that twenty-four hour monitors provided very limited information about spike levels of exposure and were unsuitable for this project. The monitors worn only at school did provide a good measure of the exposure concentration during the day. However, a better estimate was possible if monitors remained inside the classroom for their entire period of exposure. This would eliminate any dilution effect, during recess and lunch breaks, that would occur if badges were worn by children outside the classroom. Two or three stationary monitors could be placed in each classroom on a daily basis to assess the range of levels of exposures within a classroom. The small variation found between monitors worn in the same classrooms on the same day made this logical. Such monitors would accurately reflect the level of NO_2 experienced by all children in the same room. This method would also allow the inclusion of many more children into the study than would have been possible if monitors had been worn individually.

The restriction of home badge monitoring to periods of gas use was determined as the best way to assess home exposure levels. Monitors worn for

eighteen hours in non-school time failed to give an adequate estimation of daily spike levels of exposure in homes with gas appliances. To achieve this, the time and place of environmental monitoring needed to be restricted. Restriction of the exposure period to times of gas use within the home would better meet the study objective. However, because of the variation of NO_2 levels within rooms in the one household, badges would still need to be worn by children during these times. Children would be free to move from room to room within their homes. To allow for this activity, badge monitors would need to be provided with tabs that allowed them to be worn. This method was to determine the average personal level of exposure experienced by children at home during periods of gas exposure on the days monitored. It removed the need to quantify exposure levels in different rooms and use activity data to estimate level of exposure.

SYMPTOM RATES AND NITROGEN DIOXIDE EXPOSURE

Daily symptom recording was successfully completed on 79 of the 90 children who were enrolled in the study. Of these, the proportions of children who experienced different symptoms were variable, and ranged from 33 percent for wheezing to 85 percent for sore throat and runny nose. However, children from homes with unflued gas appliances were excluded from exposure classification and further analysis due to the possibility of misclassification. As mentioned previously, the protocol used made it impossible to tell if these children had experienced high levels of exposure at some time at home. Also, children whose parents smoked at home were excluded from the exposure classification.

The time-measured average atmospheric concentrations for the remaining group are shown in Table 3.4. This table shows that all the remaining 22 children from the unflued gas heated school were exposed to levels of NO_2 higher than the 21 from the electrically heated school in both groups. On this

basis, the children in the unflued gas heated school were classified as exposed, and those in the electrically heated school as controls for the purpose of analysis. Control and exposed children were delineated by heating type.

Table 3.4 also shows much higher concentrations in the exposed children that underwent school-time as opposed to twenty-four monitoring . This allowed a greater level of discrimination between exposure concentrations, which was an important issue for classification purposes in the main study.

Table 3.4 Distribution of time-measured average atmospheric concentrations used to determine exposure status of children, excluding children from gas appliance homes, included in the comparative analysis of symptom rates.

Mean average 24 hour (ppm) atmospheric concentrations for monitors worn for 24 hours		Mean average school-time (ppm) atmospheric concentrations for monitors worn at school only (6-hours)	
Control school children	Exposed school children	Control school children	Exposed school children
0.003	0.008	0.007	0.044
0.003	0.006	0.002	0.052
0.003	0.009	0.009	0.036
0.004	0.009	0.004	0.050
0.003	0.007	0.005	0.036
0.002	0.015	0.006	0.056
0.002	0.014	0.005	0.030
0.003	0.011	0.006	0.040
0.004	0.012		0.044
0.003	0.024		0.036
0.003			0.048
0.004			0.030
0.003			

The geometric means comparing symptom "rates" are shown in Table 3.5. These means represent the exponential - 1 of those derived in the analysis using the natural logarithm of the symptom ("rates" + 1) for each symptom. The plus-minus values in Table 3.5 represent the exponential - 1 of the standard errors derived in the analysis. No significant differences were observed for any symptom. This result is not unexpected for a number of reasons. The levels of exposure recorded for all children involved in the comparative analysis were well below current guidelines. As well, the statistical power to detect a

difference was recognised to be low, due to the small sample size. Comparison of health data between children was not a main objective of the pilot study, and little inference can be drawn from the lack of any consistent or statistical differences in the two small groups of exposed and control children.

Table 3.5 Geometric mean values for symptom rates between control and exposed children, with associated p values*.

Symptom	Geometric mean of exposed symptom rates (n=22)	Geometric mean of unexposed symptom rates (n=21)	p value
Sneeze	0.044 ± 0.018	0.024 ± 0.008	0.36
Stopped up nose	0.049 ± 0.015	0.054 ± 0.015	0.84
Runny nose	0.078 ± 0.016	0.073 ± 0.019	0.83
Sore throat	0.049 ± 0.007	0.045 ± 0.011	0.77
Hoarse voice	0.019 ± 0.006	0.022 ± 0.007	0.87
Dry cough	0.044 ± 0.008	0.080 ± 0.024	0.18
Cough with phlegm	0.046 ± 0.013	0.044 ± 0.012	0.91
wheeze	0.012 ± 0.005	0.019 ± 0.007	0.38

*Plus-minus values are geometric means ± exp(SE ln(symptom rate + 1)) - 1.

CONCLUSION

The pilot study provided useful information and allowed important decisions to be made. Concentration differences were shown to exist between unflued gas and non-gas atmospheres, which were capable of being accurately recorded. However, monitors worn for twenty-four hours were found unsatisfactory for this project, as it became clear that they failed to reflect daily spike levels of exposure. Placement of static monitors in classrooms was found suitable for this purpose. Separate home monitoring, restricted to times of gas use, was also suitable to reflect spike levels of exposure. However, badges would need to be worn by children to overcome the between-room variation in concentrations within homes. The manufacture and analysis of large numbers of passive diffusion badge monitors was considered possible, and daily respiratory diaries were used successfully. These observations and decisions provided the basis upon which the development of the main study protocol was undertaken.

CHAPTER 4

MAIN STUDY RESEARCH PROTOCOL

ANALYTICAL LABORATORY

Discussions were held with the State Pollution Control Commission (SPCC) of New South Wales (NSW), now called the Environmental Protection Authority (EPA), about monitoring requirements. It was planned to monitor school classrooms extensively over a four to five month period, and to include home monitoring as well. The EPA agreed to provide laboratory premises, a spectrophotometer and training of laboratory personnel. A laboratory was established and two full-time chemical technologists employed in mid-April. This laboratory was situated within the EPA at Lidcombe in Sydney, and operated until the end of September 1992.

The chemical technologists underwent a two week training period, under the direction of EPA staff who had been involved in the pilot study. During that time, they were taught to assemble and analyse passive diffusion badge monitors according to the methods described in Chapter 3.

Each week, up to eight hundred monitors were bundled into small air tight plastic bags, along with a blank and a capture badge to remove any unwanted NO_2 that might have entered the bag. Blanks were used during analysis to correct for any unwanted NO_2 that entered the bags during storage. Each bag contained monitors for one day of sampling in each school. These bags were then grouped into weekly batches for distribution. Each batch was housed in a large sealed bag, also containing two capture badges. Laboratory staff remained blind to the exposure status of all monitors.

P. Barry Ryan, Associate Professor of Environmental Health from Harvard School of Public Health, visited the study in May 1993, to review procedures.

His findings were that "The laboratory appears to be under good control. Laboratory personnel display a professional attitude and genuinely care about the quality of their work. They have adapted well to the new tasks and have developed a rapid, streamlined and efficient technique for analyzing samples. Their work load is heavy but of relatively short duration. The analysis of 800-900 samples per week results in a "full plate" but the duration of the investigation, coupled with the break half way through should minimize the effects of this difficulty."

SCHOOLS

The study was conducted in Catholic schools in NSW. State schools had previously been the subject of intensive classroom monitoring conducted by the SPCC, the results of which were reported in Chapter 2. Familiarity with the subject by teachers and parents in these schools was a potential source of bias. As well, many heaters in those schools had been modified to reduce the levels of NO_2 emission. Catholic schools, however, were known to utilise unflued gas heaters in winter and previously had not been investigated.

Western Sydney was chosen as the area in which to conduct the main study. It was close to the laboratory at Lidcombe. This closeness allowed strict time schedules to be met, which may otherwise have been disrupted by sending large numbers of monitors by courier over long distances for distribution. The climate was also appropriate. Western Sydney was an area where unflued gas appliances were known to be used, and low temperatures were expected to ensure the use of heating at school and at home for about two to three months a year. This would be long enough to collect a substantial amount of health data.

The school systems in Sydney and Canberra were very much alike. The duration of school terms and daily activities undertaken by children were

similar, as was the construction of school buildings. On this basis, the decisions arising out of the pilot study in Canberra were considered to be applicable to schools in Sydney.

Permission for the study to proceed was granted by representatives from the Catholic Education Offices of the Archdioceses of Sydney and Parramatta in December 1991. Four schools with unflued gas heated classrooms, matched with four nearby schools with electrically heated classrooms were selected, covering a geographical area from the inner west of Sydney to the lower Blue Mountains. This covered a radius of approximately one hundred kilometres. The eight schools provided a total of forty-one classrooms for air monitoring and from which to draw the study sample (Table 4.1).

Table 4.1 Classroom and heater type distribution between schools

School ID	Heater type	No. of rooms
1	Electric	5
2	Unflued Gas	4
3	Electric	5
4	Unflued Gas	6
5	Electric	5
6	Unflued Gas	5
7	Electric	5
8	Unflued Gas	6

School buildings were generally similar. They were brick buildings, up to two floors in height, with windows on two sides. Both the length and breadth of classrooms were approximately 10 metres, with ceilings up to 2.5 metres. Ryan, in the course of his visit mentioned above, estimated the overall air exchange rates for these classrooms to be less than 1.5 air changes per hour, even on very cold days when indoor-outdoor temperature differences increased the driving force for air exchange. This was important for the use of passive diffusion badge monitors, which were only suitable for use in areas where the air exchange rate was no greater than two air changes per hour.

Schools were divided into two groups for the purpose of weekly monitoring, each with two gas heated and two electric heated schools. This was necessary to reduce the monitors required on a weekly basis to a manageable number, yet still permit extensive monitoring to be made in each classroom. The classrooms from each group were monitored on alternate weeks between 27 April and 11 September 1992, over a total monitoring period of twenty weeks. This allowed for a two week vacation period after the first ten weeks. Each classroom was also monitored concurrently with hourly monitors over two of their monitored weeks. The protocol is illustrated in Figure 4.1.

Group A	Group B
Schools 1 to 4	School 5 to 8

Week	Week commencing	Group for 6-hour monitoring	School for hourly monitoring
1	27/04/92	A	None
2	04/05/92	B	None
3	11/05/92	A	1
4	18/05/92	B	6
5	25/05/92	A	2
6	01/06/92	B	5
7	08/06/92	A	4
8	15/06/92	B	7
9	22/06/92	A	3
10	29/06/92	B	8
SCHOOL HOLIDAYS			
13	20/07/92	A	1
14	27/07/92	B	6
15	03/08/92	A	2
16	10/08/92	B	5
17	17/08/92	A	4
18	24/08/92	B	8
19	31/08/92	A	3
20	07/09/92	B	7

Figure 4.1 School monitoring protocol. Schools were divided into two groups and nitrogen dioxide levels from classrooms of each group were measured daily on alternate weeks using 6-hourly monitors. Each classroom also had hourly measurements taken daily over two weeks.

For the first seven weeks, three new monitors, placed horizontally at the front, centre and rear of each classroom approximately one metre from the floor, were exposed daily for the duration (6-hours) of each school day. After

that, the number of monitors placed in electric heated classrooms was reduced to two, since variations between the monitor levels in previous weeks were consistently negligible. Apart from normal breaks and special activities, each child remained in the same classroom for the entire study period.

Two six-hour monitors were also placed in a sheltered position outside each school daily for one week. All times of monitor exposure were recorded.

THE COHORT AND DAILY RESPIRATORY DIARIES

As mentioned in chapter 3, the proportions of children who had non-zero "rates" for each symptom ranged from 33 percent for wheezing to 85 percent for sore throat and runny nose, and no significant differences were found between the control and exposed children. Based on these figures, a sample size estimation was made, assuming an estimated expected frequency of symptomatology of 50 percent in the unexposed, with an estimated small increase in expected frequency in the exposed. For a 95 percent confidence interval and a power of 80 percent, the 1:1 sample size, for a relative risk of between 1.2 and 1.25, was calculated to be between 524 and 814. The number of schools selected to participate in this study contained approximately 1100 children. Assuming an adequate response rate among these children, this number was considered sufficient to provide a representative sample for hypothesis testing. Experience in Canberra suggested that the approach used would be likely to result in adequate parental co-operation.

In early February, letters and consent forms were distributed to all children to be taken home to parents, inviting them to participate in the study by keeping daily diaries of their children's respiratory symptoms (Appendix 3). For ethical reasons, parents were informed that gas combustion was being investigated. Eight hundred and fifty parents initially agreed to participate. Of

the 250 non-responders, the non-response rates were similar between the electrically heated (30%) and unflued gas heated (27%) schools.

Daily diaries were again chosen as the method of symptom data collection (Appendix 4). Eighty-eight percent of parents maintained these diaries successfully for five months during the pilot study, an appropriate outcome for their continued use in the main study. However, the format of the diaries, not the content, was altered following a meeting between the author and Professor John Spengler, Director of Exposure Assessment and Engineering, Department of Environmental Health, Harvard School of Public Health. Professor Spengler had previously used daily diaries, developed for use with an optical scanner. This aided the input of a large amount of data and was adopted for this study. Symptoms recorded daily by parents on these diaries did not change. They were hoarse voice, sore throat, cough with phlegm, dry cough, sneezing, stopped up nose, runny nose, and wheezing. Each parent also recorded if their child had a cold or was absent from school. However, each diary contained recorded data over one week instead of one month, and parents were required to fill in the date for the week monitored. Symptoms were recorded as present only if they were bothersome to the child. Definitions were sent to parents to assist them in this process (Figure 4.2).

Four diaries were sent to parents every four weeks from March to September 1992. A telephone number was included for parents to contact staff if needed. Symptom data collection commenced four weeks prior to the commencement of atmospheric monitoring.

From 850 parents who initially agreed to participate, daily diaries were received on 635 children. Of these, 16 children were excluded because their early sets of returned diaries were blank and they subsequently dropped out of the study. Another 21 were excluded because they only returned diaries prior to the period of winter heating. For these 252 children who dropped out of the

study, the drop out rates were similar between the electrically heated (32%) and unflued gas heated (29%) schools. Satisfactory diaries were therefore received on 598 children.

HOARSE VOICE: This means that your child's voice has changed and become rough or unnaturally deep or harsh. Sometimes the voice may become so hoarse that your child cannot talk.
SORE THROAT: Your child may complain that it hurts to swallow or that his or her throat is sore. Include tonsillitis in this symptom.
COUGH WITH PHLEGM: All children cough from time to time. A cough with phlegm means that the cough sounds loose or your child brings up phlegm with the cough. Mark the circle if your child is bothered by such a cough or has a cough with phlegm that occurs a lot on that day.
DRY COUGH: If your child has a cough that is not associated with phlegm it is a dry cough. Mark the circle if your child is bothered by such a cough or has a dry cough that occurs a lot on that day.
SNEEZING: All children sneeze from time to time. Mark the circle if your child sneezes a lot or is bothered by sneezing on that day.
STOPPED UP NOSE: This refers to your child being unable to breathe through the nostrils and having to breathe through the mouth.
RUNNY NOSE: This refer to a discharge of liquid from your child's nose. This discharge may be clear, yellow or green.
WHEEZING: Wheezing refers to a whistling sound that comes from the chest when the child breathes. Breathing may be difficult in these circumstances.
HAS A COLD: Mark this circle only if you think your child has a cold on that particular day.
MISSED SCHOOL TODAY: This is only to be filled in for school days. Do not fill in on weekends or public holidays.

Figure 4.2 Symptom definitions sent to parents for recording daily diary information

THE COHORT AND RESPIRATORY HEALTH QUESTIONNAIRES

A short questionnaire to determine home smoking and gas use was distributed in May 1992 (Appendix 5). Using this information, of the 598 children with satisfactory diaries, 111 were excluded because of parental smoking at home and 62 for failure to provide information on home smoking or gas appliance use. As a result, 425 children were available for exposure classification and analysis.

Duplication in weekly numbering of diaries on any of these children resulted in the deletion of that duplicate and subsequent diaries for that child

from the data set. Even so, diaries containing ten or more weeks of data for analysis during the winter heating period were obtained for 89 percent of children from both electrically heated and gas heated schools. A "rate" for each symptom for each child was determined by expressing symptom days as a proportion of the number of recorded days of observation.

Also using the questionnaire information, a sub-sample of children were selected for home monitoring. Although emphasis was placed on sampling as many children from gas appliance homes as possible, five children from electric homes were included for comparison. Telephone contact was made with parents of children whose questionnaires indicated that they were exposed to gas appliances but not tobacco smoke. Permission was sought to undertake home monitoring over four evenings and protocol instructions were provided to parents who agreed. Monitors used for home measurements were placed in individual air tight plastic bags and sealed in a larger bag containing two capture badges and a blank. One hundred and twenty-six children, including the five from electric homes, were given sealed badge monitors to take home to be opened only by their parents. Each parent was instructed that the family should carry out typical evening activities and to expose and pin the badge monitor onto the outer garment of their child's clothing. Monitors were worn for 1 hour in homes that were all electric, or where gas was used for a shorter time period. Otherwise the monitors were worn during gas use or until bedtime if gas was used longer. All times of monitor exposure were recorded. This home protocol is thus different from that used in the pilot study, where monitors were exposed for the entire time the children were not at school.

Demographic and other background data were collected using a respiratory health questionnaire, similar to the one used in the pilot study, based on the American Thoracic Society Questionnaire (Appendix 6), but modified for use with an optical scanner. These were sent to parents in

September 1992 and followed up with a second mailout, in December 1992, to parents who had not returned the questionnaire from the first mailout.

FIELD ASSISTANTS

Recruitment and training of two field workers occurred in April 1992. The main responsibilities of these workers were to ensure accurate distribution, collection and storage of monitors, and to cross-check identification numbers and distribute daily diaries. They were required to envelope and send out diaries, and to ensure that each diary's identification number was correct for the child to whom it was sent. Two teachers from each school also assisted with field activities.

The role of the field staff in this process was critical to its success. At the time they returned a week's supply, one field worker picked up new batches of monitors from the laboratory and distributed them to the appropriate schools on the first school day of the following week. The nominated teachers then set up the monitors as required, under the supervision of the field worker who would make regular visits to check on proper placement. That field worker also conducted routine control checks on monitor labels and placement in those schools throughout the week. The other field worker spent the entire week at the school in which hourly monitoring was undertaken and managed the labelling, distribution and collection of the six-hour, hourly and home monitors.

Over 10,000 monitors were used during the study period. They were all carefully labelled using a unique code indicating the week, day, duration and time of exposure. As well, the code indicated the school, classroom, and position in which each monitor was placed (Figure 4.3). Removable adhesive labels, containing the code, were attached to the undersurface of each monitor by field workers.

Code = WK D H S R P

WK	= the week number in which monitoring took place from 1 to 20
D	= 1 to 5 from monday to friday consecutively
H	= 1 for the first hourly monitor = 2 for the second hourly monitor = 3 for the third hourly monitor = 4 for the fourth hourly monitor = 5 for the fifth hourly monitor = 6 for the sixth hourly monitor = 7 for the 6-hourly (all day) monitor
S	= the school Identification number from 1 to 8
R	= the classroom identification number from 1 to 41
P	= the position placed in the room: 1= front; 2= centre; 3 = rear of the room

Figure 4.3 Monitor label coding system

RESPIRATORY ILLNESS EPISODES

Daily diaries provided the opportunity to investigate the association between NO_2 exposure and discrete respiratory symptoms. However, it was important also to investigate the association between exposure and the occurrence of respiratory illness episodes. To do this, criteria for illness episodes, based on symptom occurrence, were developed. Criteria were similar to those used in a recent study by Samet and colleagues.[38]

A respiratory episode was defined as the occurrence, on at least two consecutive days, of any of the symptoms of hoarse voice, sore throat, cough with phlegm, dry cough, stopped up nose, runny nose, sneezing or wheezing. The end of a respiratory episode was defined as the occurrence of at least two symptom-free days. Episode duration, then, was defined as the number of days from onset of symptoms to the last day on which symptoms occurred before the occurrence of two symptom-free days.

Events were further classified into "upper" and "lower respiratory tract episodes", on the basis of cough with phlegm and wheezing. If either was present on at least one day, episodes were classed as lower respiratory tract; if absent, they were classed as upper respiratory tract. Lower respiratory tract episodes were further sub-divided as follows:

a) *Lower respiratory tract - cough with phlegm*: if wheezing was not reported during the illness episode;
b) *Lower respiratory tract - wheezing*: if wheezing was reported on at least one day.

An episode "rate", for each episode type, was calculated for each child by expressing the number of episodes as a proportion of the number of observed days. The average duration of episodes was also calculated for each child.

DATA ENTRY AND STATISTICAL ANALYSIS

The Statistical Package for Social Sciences[82] (SPSS), GLIM[83] and Epi Info[84] were used for data entry and analysis. School, home and outside NO_2 spectrophotometric absorbance levels for each badge were entered into Epi Info files and visually checked for errors. Absorbances were then converted into time-weighted average atmospheric concentrations, using the same method as described in the pilot study in chapter 3. This conversion included a correction for field blanks, temperature and atmospheric pressure and the resultant figure represented the average concentration of NO_2 in the air experienced over the period of badge exposure. Data were then exported as an SPSS file for further analysis.

Prior to scanning, diaries were visually checked for dates and completion. Any stray marks on the diaries were removed and creases unfolded. The diaries were then scanned, using an OpScan 5 scanner, which was fully compatible with, and linked to, the ScanTools application programming software. Scanned information was read directly into a ScanTools file, which was then exported as an SPSS file for analysis. Ten percent of diaries were compared visually with scanned records and all were correctly handled by the software.

Questionnaires were also scanned. The scanned data for identification number, age, gender, history of asthma and hay fever, serious illness before the age of two, parental smoking, types of heating and cooking appliances in the home, and educational level were visually checked against all questionnaires. These data were then exported as an SPSS file.

Analysis proceeded in three parts. Firstly, the patterns of NO_2 levels found within, between and outside schools were examined. Exposure levels experienced by children at home were calculated. A system was developed, using levels, to allow each child to be classified as either a control or "exposed" to NO_2. Secondly, the association between exposure classification and respiratory symptom "rates" was examined. Finally, the association between respiratory episodes and NO_2 exposure was explored.

Dr Susan Wilson, from the Centre for Mathematics and its Applications at The Australian National University, provided advice about the appropriate methods for statistical analysis. As a result, a feature of the resultant data needs to be raised before describing the analyses. First, as will be shown in the next chapter, the distribution of symptom "rates" followed no standard form. Each symptom had zero values for a large number of children. So, for each symptom, its presence/absence was examined statistically separately from its conditional (on presence) "rate". Second, there could have been significant between-subject dependence due to the (inherent) use of cluster sampling at the classroom level. However, Dr Wilson's examination of the data using quasi-likelihood functions[85] for the binary data, and inspecting the residuals from the conditional data analyses, indicated that for these data this dependence was negligible. Quasi-likelihood functions are a method of modelling the data that avoids distributional assumptions. Therefore, Dr Wilson advised that the presentation of results of complex multi-level random effects models was not warranted.

Against this background, the Student's two-tailed t-test was used to compare symptom "rates" between control and exposed children. A log transformation (ln ("rate" + 1)) was used since the distribution of the symptom "rates" was highly skewed[81], and many children did not experience particular symptoms. Then, logistic regression was used to examine whether the probability of a child experiencing each symptom differed between being exposed or a control. The Student's two-tailed t-test was then used to compare the logarithm of the non-zero "rates" for each symptom between control and exposed children.

For symptom presence found to vary significantly with exposure, potential confounding and effect modification due to age, history of severe chest illness before the age of two, hay fever, allergies and asthma, the presence of pets in the home, parental education level and geographical region were explored by comparing risk estimates between strata and by comparing crude and Mantel-Haenszel adjusted relative risks. Non-zero symptom "rates" found to vary significantly with exposure were examined within strata defined by potential confounding and effect modifying variables, and multiple linear regression analysis was used to control for confounding and to examine for effect modification.

In order to investigate a dose response relation, for those symptoms found significant for exposure, generalised regression analyses were performed between symptom presence/absence and recorded NO_2, as well as between conditional "rates" and recorded NO_2 levels. To ensure consistency in daily duration of exposure, only children from non-gas homes were included in this analysis. Separate analyses were conducted for children from all classrooms and then for children from only gas classrooms.

Sensitivity analyses were also conducted using the Student's two-tailed t-test to compare symptom "rates" between control and exposed children to

investigate a dose response relationship based upon their range of school and home NO_2 exposure. The proportion who experienced each symptom were similarly compared using relative risk estimates.

Respiratory episodes were next examined. Logistic regression was used to examine whether the probability of a child having a respiratory illness episode differed between being exposed or a control. Student's t-test was used to compare the logarithm of non-zero episode "rates" between control and exposed children. Student's t-test was also used to compare the logarithm of the mean duration of non-zero episodes. For episode presence/absence, non-zero episode "rates" and duration found to vary significantly with exposure, possible confounding and effect modification by the variables stated above were examined.

The presentation of results extends over the next two chapters. Chapter 5 focuses on NO_2 concentrations measured in schools and homes, and describes the system of exposure classification. Chapter 6 then links this classification with health data and explores the association between exposure and effect.

CHAPTER 5

NITROGEN DIOXIDE ANALYSIS AND EXPOSURE CLASSIFICATION

This chapter provides a detailed analysis of recorded atmospheric nitrogen dioxide levels. Firstly, school concentrations, according to the categories of classroom, heater type, and school are discussed. This discussion highlights the potential for misclassification of exposure status, dependent upon these categories. Then, a comparison is made between the mean one-hour maximum NO_2 level recorded in each classroom and the mean six-hour level recorded in the same classroom. This comparison aims to clarify the relationship between maximum hourly concentrations and six-hour exposures. Following this, concentrations experienced inside homes and outside schools are reported. Finally, based on these data, a classification for exposure is proposed for the purpose of respiratory symptom and episode comparisons.

ANALYSIS OF SCHOOL MONITORS

The distributions of monitors used to measure NO_2 levels in classrooms are shown in Appendices 7 and 8. There were 4,587 six-hour and 5,888 hourly monitors exposed across forty-one classrooms over a twenty week monitoring period. Less monitors were used in the electrically heated than in the gas heated classrooms. This resulted from a reduction in the number of monitors, from three to two, in electrically heated classrooms from week eight onwards. The reasons for this reduction were explained in Chapter 4.

Results of six-hour classroom monitoring

Six-hour atmospheric NO_2 concentrations were graphed for each classroom over the twenty week monitoring period (Figures 5.1 to 5.4). They clearly showed that weeks 4 to 18, henceforth referred to as the winter heating

period, constituted the most uniform period of NO_2 exposure across the gas heated classrooms. This was highlighted by the overall mean six-hour average concentrations for each classroom, calculated separately for weeks 1 to 3, 4 to 18 and 19 to 20 (Table 5.1). Prior to week 4, the mean levels were similar in all classrooms, the highest being 0.03 ppm. During the period of gas heating (weeks 4 to 18), nearly all the gas heated classrooms had levels higher than those heated electrically. After week 18, the levels in many gas heated classrooms had dropped to those recorded during the pre-gas heating period.

Table 5.1 Mean 6-hour average concentration for each classroom for the monitoring periods shown.

Electrically heated classrooms				Unflued gas heated classrooms			
	Mean 6-Hour Conc. in ppm				Mean 6-Hour Conc. in ppm		
Room No.	Weeks 1-3	Weeks* 4-18	Weeks 19-20	Room No.	Weeks 1-3	Weeks* 4-18	Weeks 19-20
School 1				School 2			
1	0.020	0.020 (0)	0.010	6	0.023	0.065 (19)	0.033
2	0.026	0.023 (1)	0.011	7	0.017	0.050 (12)	0.015
3	0.022	0.021 (0)	0.008	8	0.021	0.065 (17)	0.019
4	0.023	0.023 (0)	0.011	9	0.017	0.072 (22)	0.030
5	0.021	0.023 (1)	0.010	School 4			
School 3				15	0.012	0.057 (16)	0.010
10	0.018	0.014 (0)	0.011	16	0.015	0.064 (17)	0.011
11	0.025	0.014 (0)	0.011	17	0.010	0.051 (15)	0.007
12	0.016	0.012 (0)	0.010	18	0.011	0.053 (12)	0.059
13	0.021	0.013 (0)	0.014	19	0.016	0.116 (23)	0.053
14	0.017	0.016 (0)	0.013	20	0.014	0.031 (7)	0.009
School 5				School 6			
21	0.018	0.011 (0)	0.007	26	0.014	0.029 (6)	0.007
22	0.016	0.010 (0)	0.007	27	0.014	0.023 (3)	0.011
23	0.017	0.011 (1)	0.006	28	0.017	0.033 (7)	0.012
24	0.016	0.013 (1)	0.005	29	0.016	0.021 (2)	0.005
25	0.017	0.011 (0)	0.007	30	0.015	0.018 (2)	0.004
School 7				School 8			
31	0.011	0.008 (0)	0.004	36	0.028	0.132 (27)	0.137
32	0.011	0.008 (0)	0.003	37	0.031	0.077 (24)	0.085
33	0.010	0.007 (0)	0.003	38	0.015	0.060 (18)	0.060
34	0.012	0.008 (0)	0.003	39	0.015	0.101 (25)	0.103
35	0.012	0.008 (0)	0.004	40	0.012	0.072 (28)	0.046
				41	0.015	0.076 (25)	0.036

* Bracketed values are the number of days on which the measured NO_2 levels exceeded 0.04 ppm.

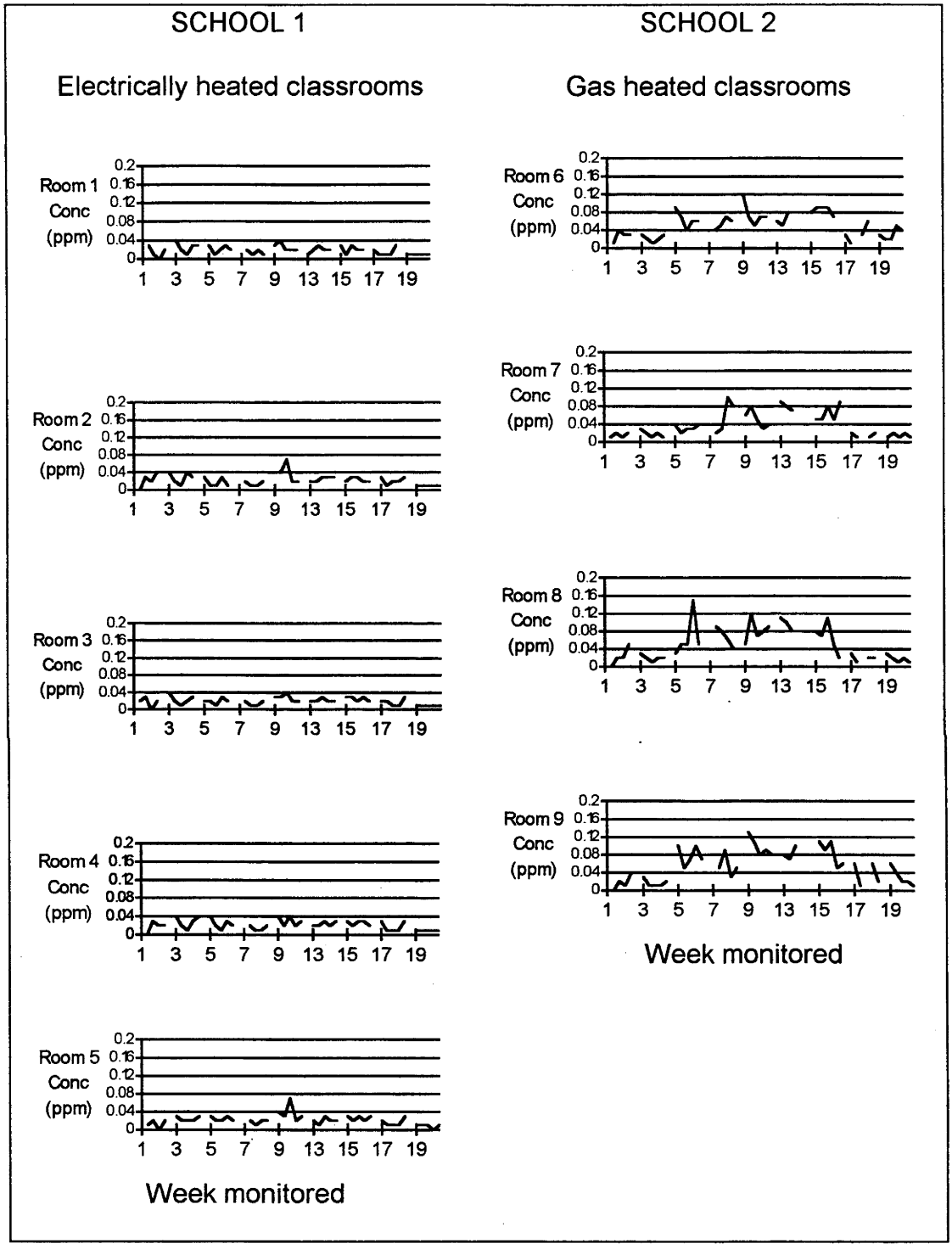


Figure 5.1 Mean daily concentration of nitrogen dioxide measured in each classroom of schools 1 and 2 over nine alternate weeks. Monitoring commenced in the first week of the total monitoring period.

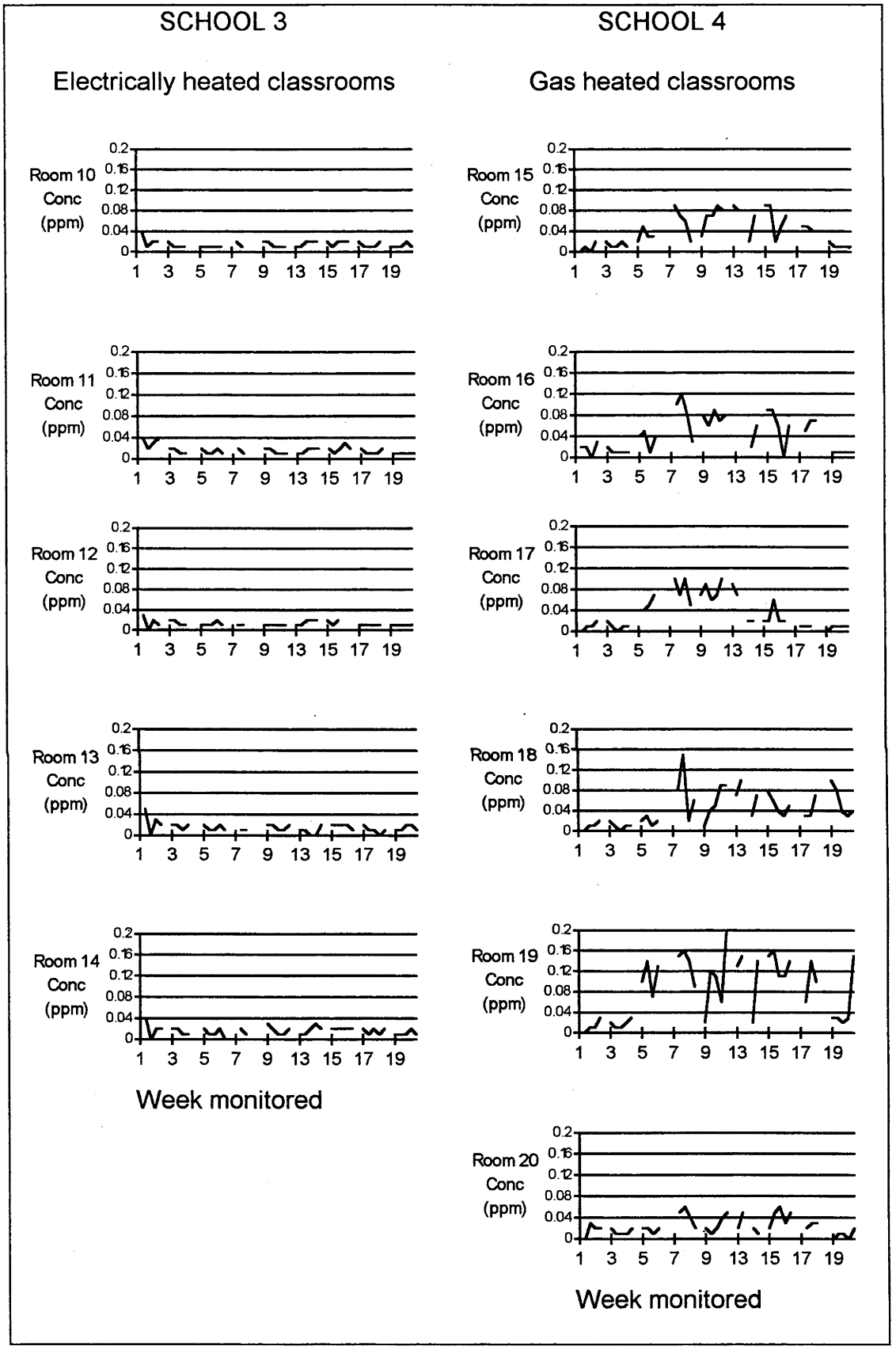


Figure 5.2 Mean daily concentration of nitrogen dioxide measured in each classroom of schools 3 and 4 over nine alternate weeks. Monitoring commenced in the first week of the total monitoring period.

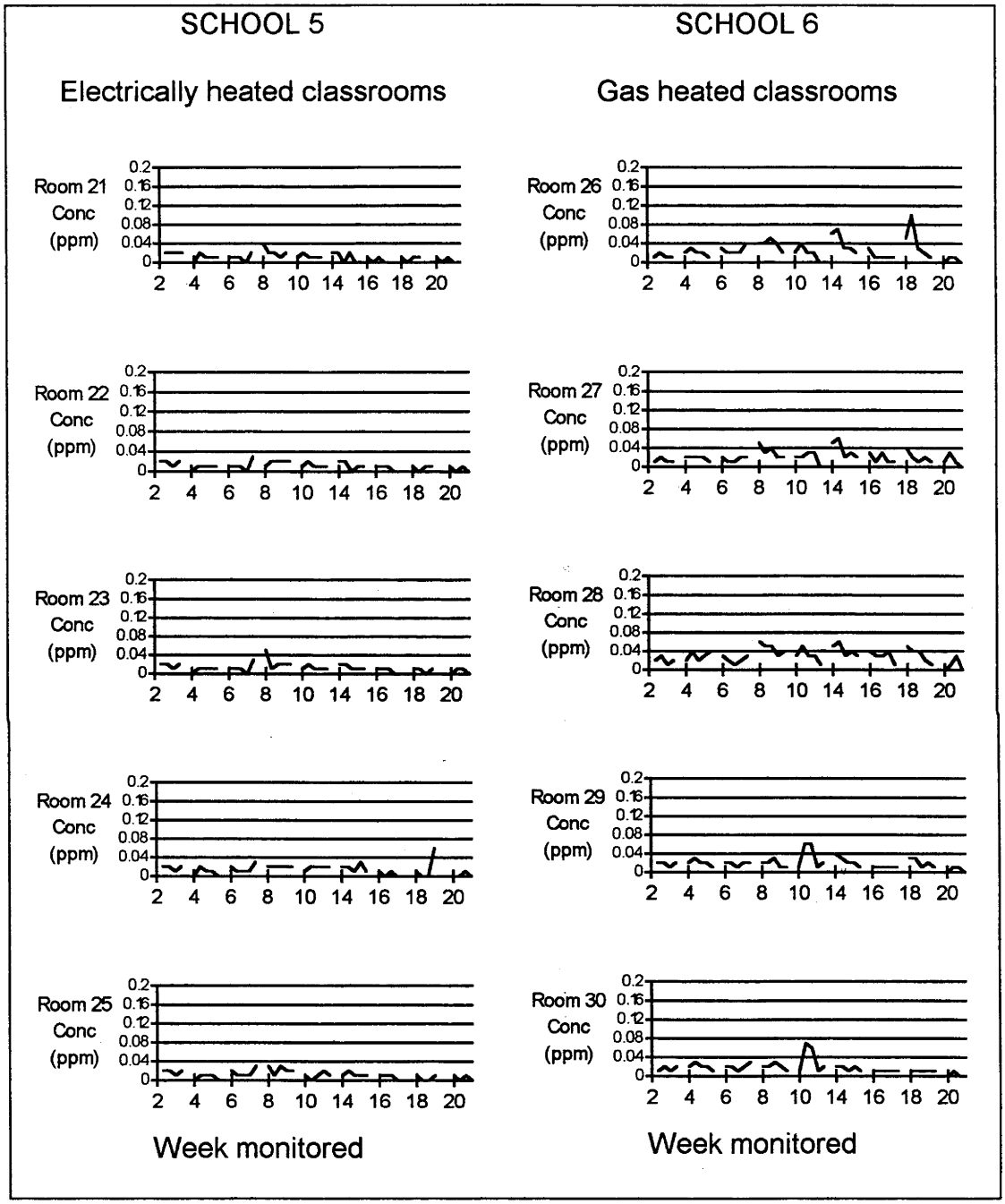


Figure 5.3 Mean daily concentration of nitrogen dioxide measured in each classroom of schools 5 and 6 over nine alternate weeks. Monitoring commenced in the second week of the total monitoring period.

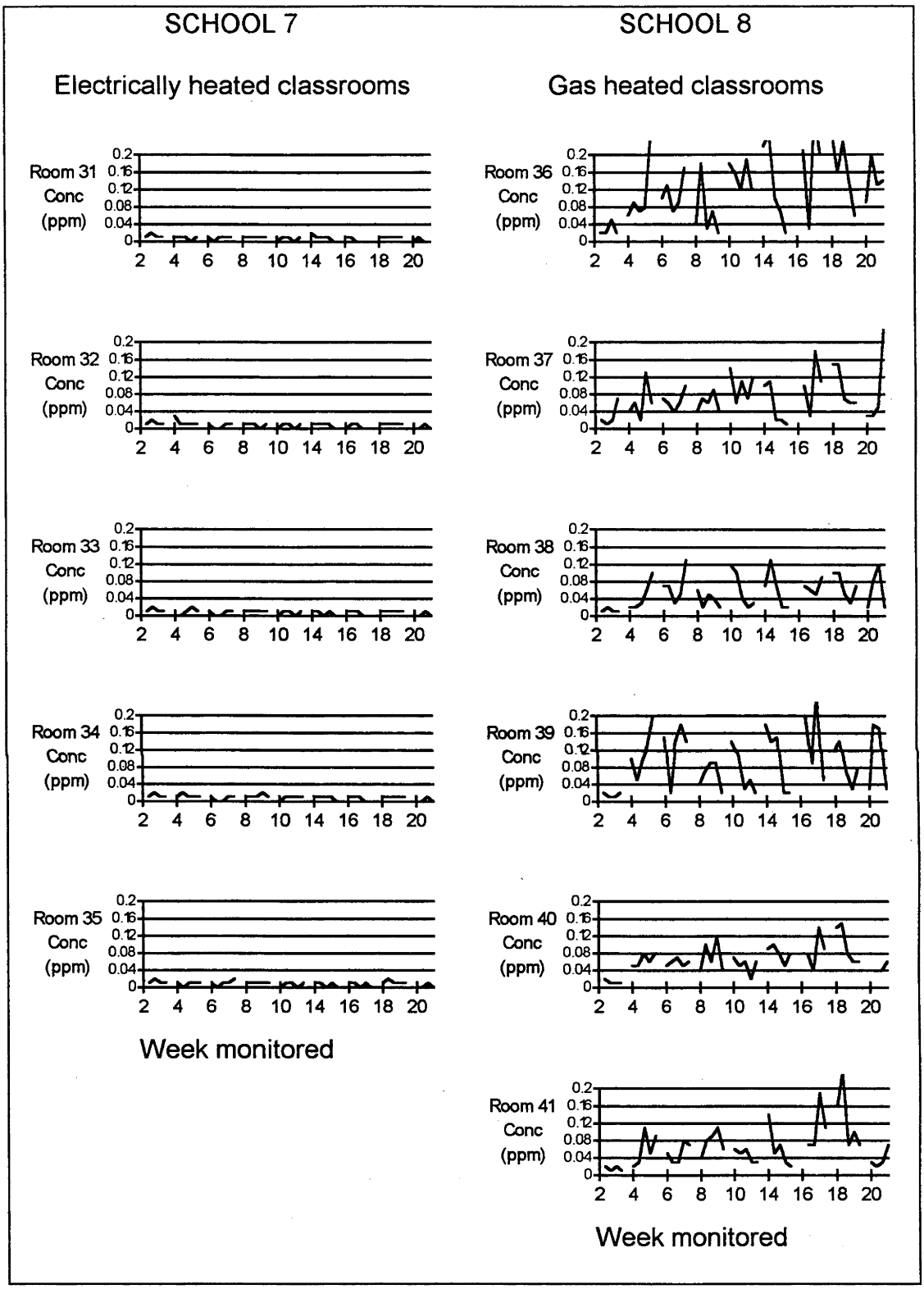


Figure 5.4 Mean daily concentration of nitrogen dioxide measured in each classroom of schools 7 and 8 over nine alternate weeks. Monitoring commenced in the second week of the total monitoring period.

The low levels found in school 6 (classrooms 26 to 30), over the winter heating period, were explained by the use of radiant gas heaters. The flames from these heaters were burnt against perforated ceramic surfaces, which have been shown to reduce the level of atmospheric nitrogen dioxide production.[74] This was in contradistinction to the much higher levels found in other gas heated schools, in which free-standing flames of convection gas heaters were used to generate heat. The low level found in classroom 20 was explained by a low level of heater utilisation. The noticeably higher levels in classrooms in school 8 were associated with lack of recent maintenance of heaters.

Examination of Figures 5.1 to 5.4 and Table 5.1 shows that measured daily levels in the twenty electrically heated classrooms were almost all equal to or less than 0.04 ppm. In contrast, daily levels in the unflued gas heated classrooms ranged from similarly low levels in some classrooms in school 6, to levels in excess of 0.20 ppm in school 8. These observations will again be discussed later in this chapter, when considering the classification of exposure.

Misclassification

At this point, attention will be directed to the mean concentrations recorded during the winter heating period, according to the type of heating used and the school attended. The overall mean concentration of six-hour monitors exposed in unflued gas heated classrooms was statistically significantly higher than that of monitors exposed in electrically heated classrooms (Table 5.2). This result is consistent with the higher production of NO_2 from unflued gas combustion.

Table 5.2 Mean nitrogen dioxide concentrations of 6-hour school monitors according to type of heating used*

Type of heating	Mean conc. (ppm)	
Electricity (n=2593)	0.01 ± 0.003	
Unflued gas (n=1994)	0.06 ± 0.03	$p < 0.001$

* Plus-minus values are the standard deviations

Further, the mean six-hour concentrations were calculated for all measured days in each school during the winter heating period, and school means were then compared. Seventeen of the 28 pairs showed statistically significant differences (Table 5.3). Gas schools numbered 4,2 and 8 had overall mean six-hour NO_2 levels statistically significantly higher than the electrically heated schools and unflued gas heated school 6. As well, the level in school 8 was statistically significantly higher than those in schools 4 and 2. The level in gas school number 6 was not statistically different from those in the electric schools. The likely reason for this low level has already been discussed.

Table 5.3 Comparisons of the means of all winter period 6-hour NO_2 concentrations for each school

School ID	Mean	School ID							
7	0.008	7							
5	0.012		5						
3	0.014			3					
1	0.022				1				
6♦	0.025					6			
4♦	0.062	*	*	*	*	*	4		
2♦	0.063	*	*	*	*	*		2	
8♦	0.086	*	*	*	*	*	*	*	8

* denotes pairs of groups significantly different at the 0.05 level
♦ denotes gas school

When these results, based solely on heating type or school attended, are compared with those found at the classroom level (Table 5.1), the potential for misclassification of exposure, based on school heating systems, becomes obvious. Not all unflued gas heated classrooms or schools had levels significantly higher than those found in electrically heated classrooms or

schools. As well, the average level found in classroom 20 was not significantly higher than those found in electrically heated classrooms, even though the average for school 4 was higher. Yet, as described in Chapter 2, the majority of past epidemiological studies have based their classification of exposure on the presence or absence of gas appliances, without objective measurements of NO_2. This finding raises doubts about the conclusions from many past studies and underlines the need for measurement of actual exposure in future epidemiological studies.

Results of hourly classroom monitoring

Maximum hourly concentrations of NO_2, present in classrooms each day over two separate weeks, were determined by hourly classroom monitoring. Classrooms in schools 3, 4 and 9 were monitored over less than ten days, due to the occurrence of a public holiday and pupil free days. These classrooms were monitored over 8, 7 and 9 days respectively. The frequency distributions of these daily maximum hourly concentrations for electrically heated and unflued gas heated classrooms are shown in Figure 5.5.

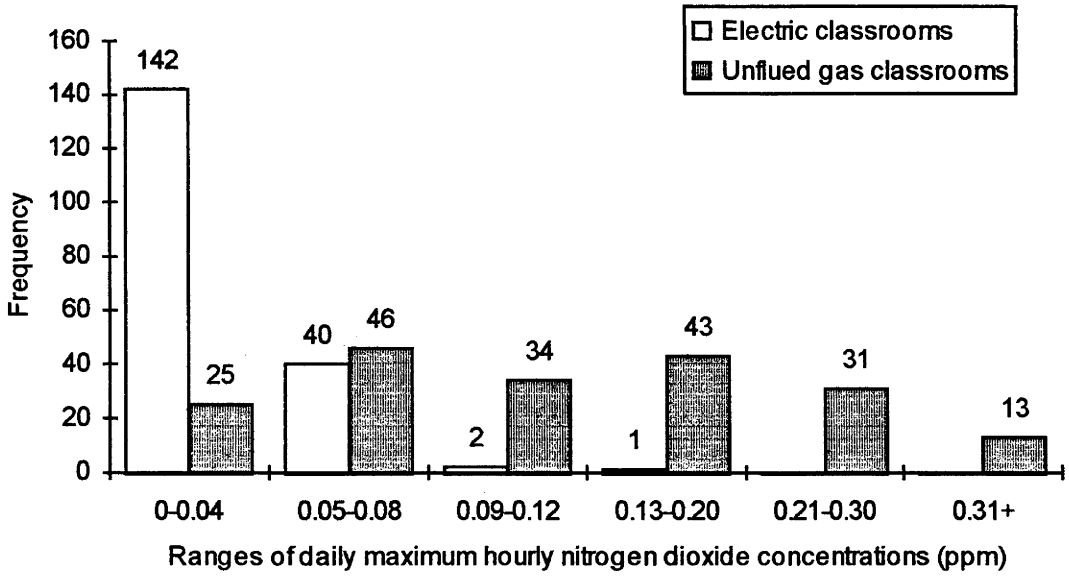


Figure 5.5 Frequency distributions of the daily maximum hourly concentrations for the electric and unflued gas classrooms

The maximum hourly concentrations of NO_2 experienced in the electrically heated classrooms were less than the World Health Organization's (WHO) recommended one hour goal of 0.21 ppm and the National Health and Medical Research Council's (NHMRC) recommended maximum hourly level of 0.3 ppm. The maximum hourly levels measured in the unflued gas heated classrooms, on the other hand, were considerably higher, and exceeded the WHO recommended level on twenty-three percent and the NHMRC level on seven percent of days measured. The highest measured level was 0.68 ppm.

The means of these maximum hourly concentrations for each unflued gas heated classroom were also compared with the means of their corresponding six-hour concentrations, measured over the same two weeks (Figure 5.6). Only classrooms in which the maximum hourly levels exceeded 0.08 ppm were included. This excluded levels below the one-hour limit of detection of these monitors.

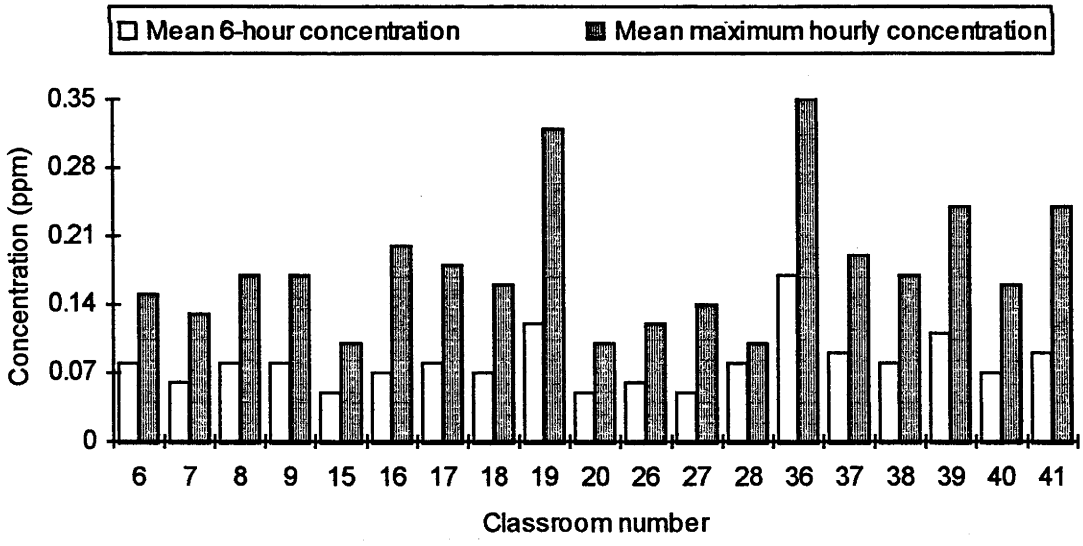


Figure 5.6 Mean maximum hourly and mean 6-hour average atmospheric concentrations for classrooms with maximum hourly levels greater than 0.08 ppm.

The mean of the ratios of maximum hourly to six-hourly average was 2.19, with a standard deviation of 0.34. How does this relate to setting a one hour goal for NO_2? In this study, NO_2 was measured in classrooms over six hours. If daily

school monitors had been exposed for twenty-four hours, including periods when children were not exposed to gas, the average atmospheric concentrations recorded would have been considerably lower. This was shown to be the case in the 1991 pilot study described in Chapter 3. In the setting of air quality guidelines, a one-hour maximum goal for NO_2 should thus be at least twice the twenty-four hour recommended goal, and when the proportion of time spent in NO_2 affected premises is low, the ratio is likely to be high. This is the case for the goals established by the WHO, which are currently set at 0.21 ppm and 0.08 ppm respectively.

ANALYSIS OF HOME MONITORS

Home monitoring was conducted in 126 homes. Badge exposure times in these homes varied from between one to sixteen hours, for reasons explained in Chapter 4. Because of the differing times of exposure, the levels recorded by home monitors were referred to as timed-average atmospheric concentrations. All five homes with electric appliances recorded mean timed-average levels of NO_2 less than 0.04 ppm. This was consistent with the results of monitoring carried out in electric classrooms. The distribution of concentrations found in the 121 unflued gas appliance homes is shown in Figure 5.7

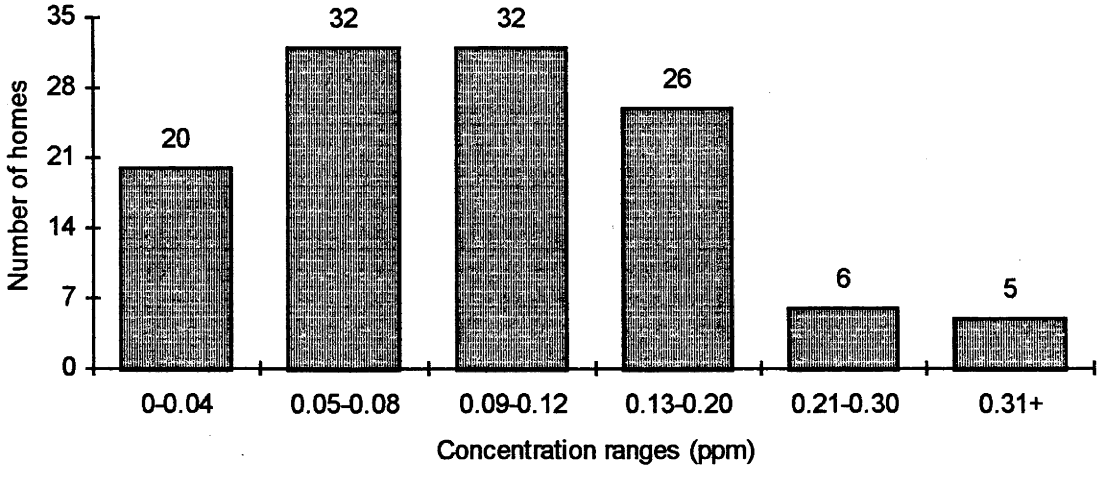


Figure 5.7 Distribution of homes with gas appliances over the mean daily timed-average concentration

Nine percent of these homes had timed-average levels of NO_2 in excess of the WHO recommended one-hour goal of 0.21 ppm.

ANALYSIS OF OUTSIDE MONITORS

Ambient levels of NO_2 measured outside the eight schools were low (Table 5.4). These levels were of the same order of magnitude as those found in electrically heated classrooms and homes.

Table 5.4 Mean concentrations of NO_2 for the 6-hour monitors placed daily outside each school for 1 week.*

School ID	Mean Concentration(ppm)
1	0.01 ± 0.01
2	0.03 ± 0.01
3	0.01 ± 0.01
4	0.01 ± 0.01
5	0.01 ± 0.01
6	0.02 ± 0.01
7	0.01 ± 0.01
8	0.01 ± 0.01

*Plus-minus values are the standard deviations

CLASSIFICATION OF EXPOSURE

Prior to the analysis of the health data, it was important to classify exposure to NO_2. The uniformly low levels in the electrically heated classrooms during the winter heating period, and in all classrooms outside this period, indicated 0.04 ppm of NO_2 as an appropriate level around which to propose an exposure classification. Examination of the mean classroom six-hour concentrations reveals a background level in the non-gas atmospheres of the order of 0.02 ppm or less (Figure 5.8). Figures 5.1 to 5.4 reveal these background levels were consistent over the winter heating period. Six-hour unflued gas heated classroom levels were widely distributed. As discussed previously, maximum hourly levels in unflued gas heated classroom were at least twice the 6-hourly averages. Therefore average levels above 0.04 ppm in these classrooms would be associated with spike levels of the order of 0.08

ppm and above. While the absolute concentrations were lower than those used in the animal experiments described in Chapter 1, this cut off provided a ratio of the order of 4:1 (0.08:0.02) or greater for spike to background atmospheric concentrations, that was consistent with the pattern of exposures used in the animal studies.

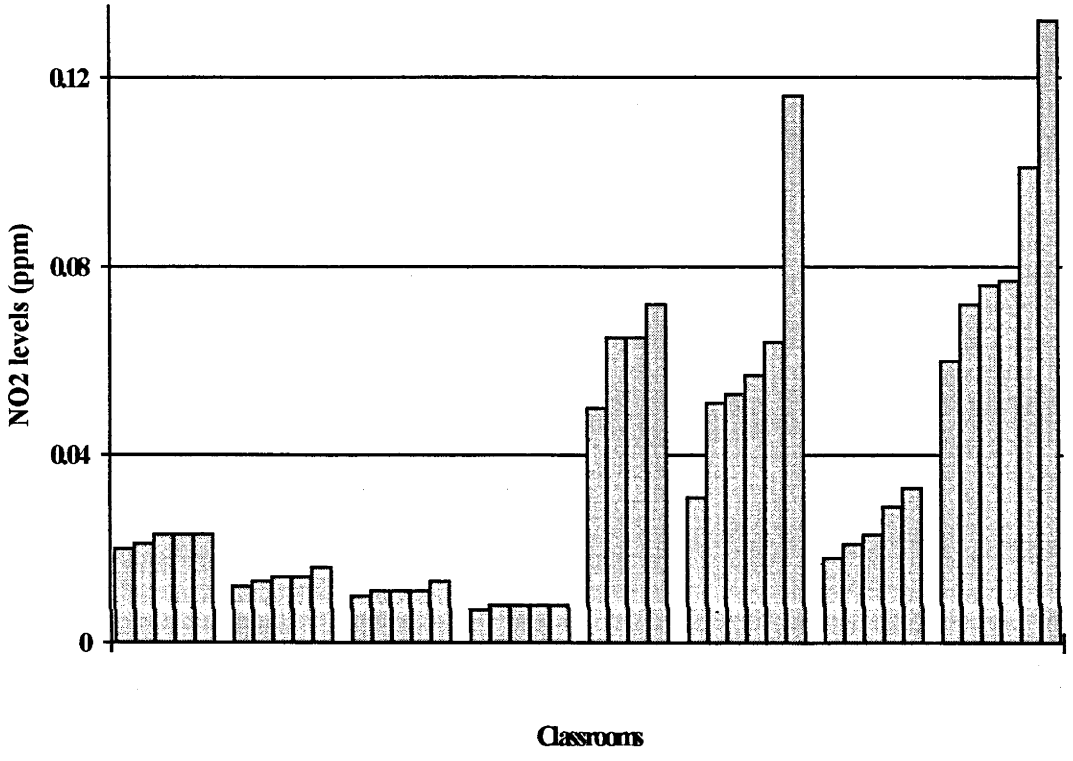


Figure 5.8 Mean 6-hour nitrogen dioxide concentration (ppm) for each classroom over the winter heating period. The twenty classrooms on the left were electrically heated. The twenty-one on the right were unflued gas heated. Each block of classrooms belonged to the same school.

A similar pattern would have been expected with unflued gas exposure at home. To achieve average home exposure levels above 0.04 ppm must have involved higher spike levels. At home, children wore the monitors on their clothing. As they moved to rooms with differing NO_2 levels, spike levels at least of the order magnitude of unflued gas classrooms would have been required in order to achieve the average levels that were observed on the monitors.

Children are now separated into exposure groups based on the level of 0.04 ppm (Table 5.5). Firstly, those children from gas appliance schools or homes, with levels above 0.04 ppm either at school or at home were classified as exposed. This included 193 children from unflued gas classrooms in which the 6-hour average atmospheric concentrations were greater than 0.04 ppm on at least five days. This criterion was selected to ensure that daily exposure was distinctly higher in the exposed than in the control group, and ranged from just above 0.04 ppm to much higher levels. Based on this distinction, all children from the schools numbered 2,4 and 8, as well as children from classrooms numbered 26 and 28 from school number 6, were classified as exposed (Table 5.1). The exposed group also includes two children with home mean-timed average levels above 0.04 ppm although they were located in unflued gas classrooms (27,29 and 30) in which the NO_2 level did not rise above the criterion level. The exposed group also included the 49 children from electrically heated schools but gas appliance homes, with home mean timed-average NO_2 levels greater than 0.04 ppm. In all, there were 244 children in the exposed group.

The control group consisted of 105 children from electrically heated schools without exposure to gas combustion at home.

Thirty four children from electric schools, with measured home gas levels less than 0.04 ppm or whose homes were unmeasured, were excluded on the basis of uncertain exposure associated with limited information. (Resources did not permit a more extensive home monitoring procedure.)

There remains a group of 40 children from unflued gas heated classrooms 27, 29 and 30 where the exposure levels are below the 0.04 ppm criterion. Of these only two were exposed to home gas appliances and both had measured levels below the criterion level. This group is considered to have an uncertain or intermediate exposure level between the control and exposed groups.

This classification system had a number of advantages and disadvantages. According to the definition of exposure used in this study, misclassification of spike exposures was unlikely among the control and exposed children. This was achieved at the expense of sample size, reduced by the need to exclude children of uncertain exposure. However, rather than weaken the power of the analysis by considering three exposed groups, the analysis is carried out by comparing the exposed group to the control group and then by similar comparisons with the intermediate group included as either 'controls' or 'exposed'.

Table 5.5 Exposure classification*

School heating	Home heating	Number of children	Exposure classification
Electric	Gas > 0.04 ppm	49	Exposed
Electric	Gas < 0.04 ppm	36	Excluded
Electric	No gas	105	Controls
Gas > 0.04 ppm	Gas or no gas	193	Exposed
Gas < 0.04 ppm	Gas > 0.04 ppm	2	Exposed
Gas < 0.04 ppm	Gas < 0.04 ppm	2	Uncertain
Gas < 0.04 ppm	No gas	38	Uncertain
Total number of children		425	

*Gas exposure with levels above 0.04 ppm either at school or at home was set as the criterion for exposure. Uncertain and exclusion categories involved gas exposure at levels < 0.04 ppm.

CONCLUSION

Children were classified as controls or exposed according to their daily recorded NO_2 levels in their classroom and home. A level above 0.04 ppm, either at school or at home, was set as the criterion for exposure. Misclassification among children so classified was thought to be unlikely in view of the accuracy of the monitoring instrument. Accordingly, 105 control, 244 exposed and 40 children of uncertain exposure were provided for comparative analyses. At the present time, air quality guidelines have been set by the WHO and NHMRC, which are well above 0.04 ppm. These guidelines mainly resulted

from the results of controlled human exposure studies, the limitations of which were discussed in Chapter 2. Epidemiological studies have generally not contributed to these guidelines. This study, however, provided the opportunity to examine the association between quantified levels of exposure often experienced in the current Australian environment and their health effects.

CHAPTER 6

NITROGEN DIOXIDE AND RESPIRATORY HEALTH EFFECTS

Respiratory symptomatology formed the basis upon which to examine the association between NO_2 exposure and respiratory illness. Hoarse voice, sore throat, cough with phlegm, dry cough, stopped up nose, runny nose, sneezing and wheezing, "has a cold" and "absent from school", were separately examined. To do this, a "rate" for each symptom for each child was determined by expressing symptom days as a proportion of the number of recorded days of observation. As well, respiratory symptoms were combined, according to predetermined criteria, to form respiratory episodes. The presence of any symptom on at least two consecutive days, followed by at least two consecutive symptom-free days, constituted the illness episode. If cough with phlegm or wheezing was present, an episode was classified lower respiratory; if not, it was called upper respiratory. A lower respiratory tract episode without wheezing was called *lower respiratory tract - cough with phlegm*. If wheezing was present, it was called *lower respiratory tract - wheezing*. An episode "rate" was calculated for each child by expressing the number of episodes as a proportion of the number of observed days. The average duration of episodes was also calculated for each child.

Parents were required to maintain symptom diaries on their children for six months. It is possible that temporal bias in reporting may have occurred. However, 80% of parents from both the exposed and control groups maintained diaries throughout, and the drop out rate was proportionally equal between the two groups across the winter heating period (Figure 6.1).

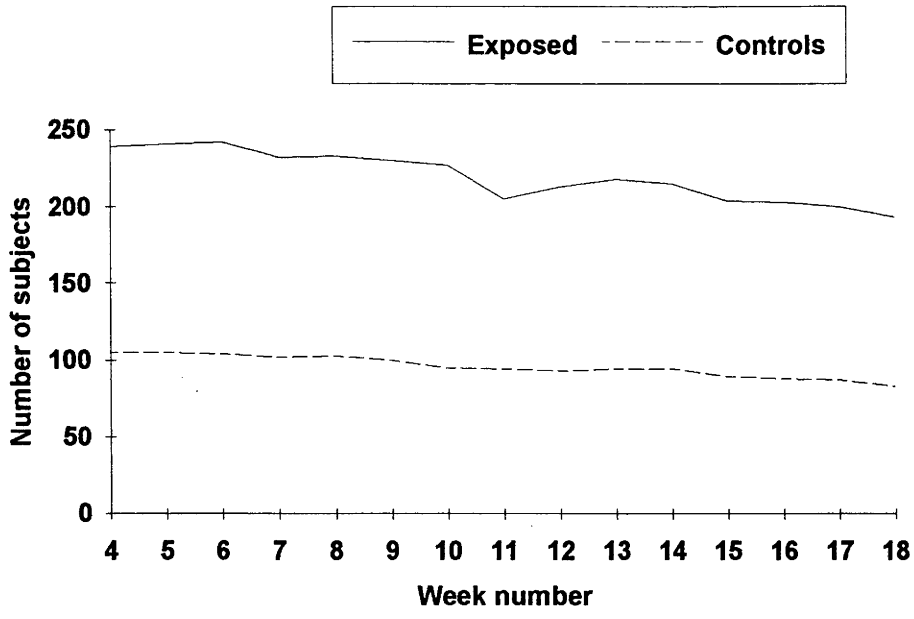


Figure 6.1 Temporal reporting of symptom diaries by parents during the winter heating period

For comparative analyses, three groups of children were identified. Children who experienced levels of NO_2 above 0.04 ppm, produced by gas appliances either at school or at home, were classified as exposed. Controls, on the other hand, had no known gas exposure and were exposed to background levels of NO_2 of the order of 0.02 ppm and below. A third group were identified who were exposed to unflued gas heating at school, but whose measured NO_2 exposures were almost always less than 0.04 ppm. The classification of these children was considered uncertain because they were known to be exposed to the products of unflued gas combustion over the winter heating period.

DISTRIBUTIONS OF SYMPTOM "RATES"

The distributions of the "rates" of sore throat for the 349 children classified as controls and exposed are shown in Figure 6.2. The patterns shown were similar for all symptoms and followed no standardised form. There was a large, but variable, number of zero "rates" for each symptom among both

the control and exposed children, and the frequency diminished as the "rates" increased.

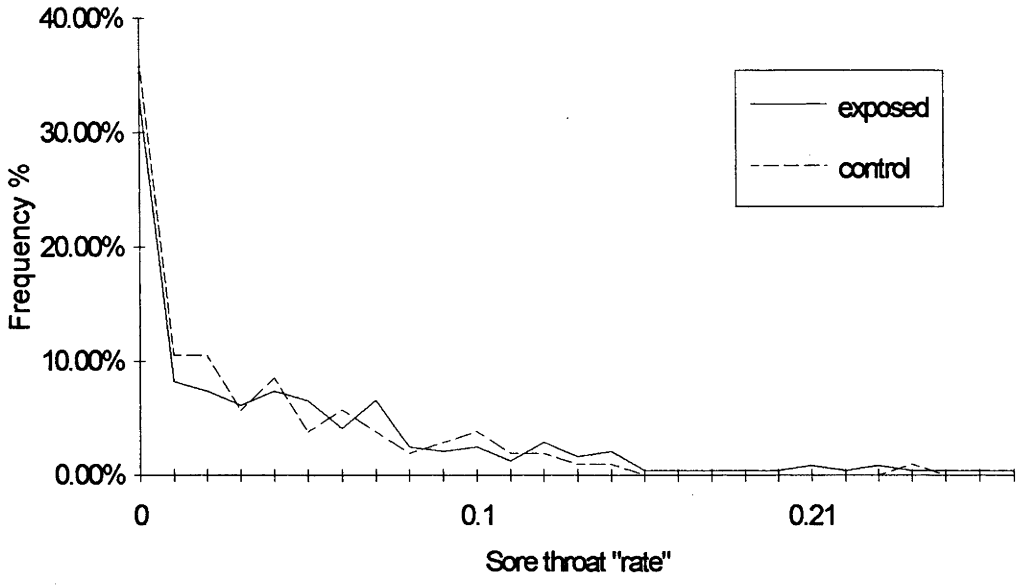


Figure 6.2 Frequency (%) distribution of the "rates" of sore throat for control and exposed children.

Many children did not experience individual symptoms. To take account of this, apart from an analysis of overall "rates", separate analyses were conducted on the proportion of children who experienced each symptom, and on the "rates" in those children in whom symptoms occurred.

SYMPTOMS AND EXPOSURE TO NITROGEN DIOXIDE

The geometric mean symptom "rates" of the control and exposed children are shown in Table 6.1. Symptom "rates" for sore throat, cough with phlegm, wheeze, the presence of a cold and absenteeism from school were statistically significantly higher in the exposed than control children. The same trend was observed for dry cough. No differences were found for other symptoms.

Table 6.1 Geometric mean values for the natural log of individual symptom rates (plus one) between the control and exposed children

Symptom	Control Mean (n=105)	Exposed Mean (n=244)
Hoarse voice	0.008	0.012
Sore Throat	0.033	0.045 *
Cough with phlegm	0.037	0.062 **
Dry cough	0.068	0.079
Sneeze	0.027	0.030
Stopped up nose	0.053	0.054
Runny nose	0.078	0.074
Wheeze	0.007	0.016 *
'Cold'	0.041	0.068 **
Absent from school	0.014	0.025 **

* $0.01 \leq p \leq 0.05$
** $p < 0.01$

Symptom "rates" were also compared following the inclusion of the 40 children of uncertain classification. When included as 'exposed', the level of statistical significance for sore throat, cough with phlegm, wheeze, presence of a cold and absenteeism increased. No significant differences were found for other symptoms. When included as 'controls', only cough with phlegm and absenteeism remained statistically significantly higher in the exposed children. No significant differences were found for other symptoms. These changes indicated that appreciable excess symptomatology occurred in those exposed to very low levels of NO_2 associated with unflued gas combustion.

Analysis of symptom presence/absence and non-zero symptom "rates"

The proportion of children with non-zero "rates" for absenteeism was significantly higher in the exposed than the control group, and was of borderline significance for the presence of a cold (Table 6.2).

Proportions were also compared following the separate inclusion of the 40 children of uncertain classification. Firstly, when treated as 'exposed', the presence of a cold and absenteeism remained significantly higher in the

exposed children, at a higher level of significance. Then, when treated as 'controls', the presence of absenteeism only remained significant. This indicated that an excess of these children, whose exposure was uncertain, experienced the presence of cold and absenteeism.

Table 6.2 Proportion of exposed and control children with non-zero symptom "rates" for each symptom

Symptom	Control (n = 105)	Exposed (n = 244)
Hoarse voice	0.21	0.28
Sore Throat	0.64	0.67
Cough with phlegm	0.49	0.57
Dry cough	0.66	0.72
Sneeze	0.47	0.43
Stopped up nose	0.59	0.58
Runny nose	0.75	0.67
Wheeze	0.12	0.20
'Cold'	0.55	0.66 (*)
Absent from school	0.47	0.63 *

* $p \leq 0.05$ (*) = Borderline significance

The geometric mean "rates" for the control and exposed children, with non-zero "rates" for each symptom, are shown in Table 6.3. Symptom "rates" for sore throat and cough with phlegm were statistically significantly higher in the exposed children than in controls. The "rate" for cold was also higher in the exposed children. No differences were found for other symptoms.

Non-zero symptom "rates" were also compared following the separate inclusion of the children of uncertain classification who had non-zero symptom "rates". When included as 'exposed', the level of significance for sore throat and cough with phlegm increased, and for a cold reached statistical significance. When included as 'controls', no significant differences were found for any symptom. Again, this suggests that appreciable symptomatology occurred with exposure to low levels of NO_2 associated with unflued gas combustion.

Table 6.3 Geometric mean values for the natural log of individual symptom "rates" (excluding individuals with zero "rates" for each symptom) between the exposed and control children

Symptom	Control mean	Exposed mean
Hoarse voice	0.029 (n=22)	0.028 (n=69)
Sore Throat	0.038 (n=67)	0.049 (n=163) *
Cough with phlegm	0.054 (n=51)	0.076 (n=140) *
Dry cough	0.073 (n=69)	0.073 (n=175)
Sneeze	0.038 (n=49)	0.044 (n=106)
Stopped up nose	0.064 (n=62)	0.058 (n=141)
Runny nose	0.067 (n=79)	0.074 (n=163)
Wheeze	0.049 (n=13)	0.048 (n=48)
'Cold'	0.060 (n=58)	0.073 (n=161)
Absent from school	0.024 (n=49)	0.029 (n=154)

* $p \leq 0.05$

In summary, exposure was positively associated with the proportion of children who experienced a cold and absenteeism, but was not associated with increased "rates" in those affected. On the other hand, the "rates" of sore throat and cough with phlegm were positively associated with exposure, but the proportions of children were not affected. The proportion of children with non-zero "rates" for wheeze was higher among the exposed children (Table 6.2).

Multivariate analysis

A number of variables were explored for their possible confounding and effect modification of the association between exposure and the symptoms found significant for exposure.

Age was included because of a reported increase in susceptibility to respiratory infection in younger children.[86] Since the ages of children in this study ranged from 6 to 11, two categories (6-8 and 9-11 years) were identified for analysis.

Hay fever and allergy were included as surrogates for atopy which is associated with nasal symptoms and wheezing. Asthma was included because

of its association with wheezing and cough. Severe chest illness before the age of two was included because it has been associated with higher rates of respiratory morbidity in childhood[86], and associated with NO_2 exposure and increased respiratory illness.[22]

Low socioeconomic status was included because of its association with increased susceptibility to acute lower respiratory infection in children.[86] Highest level of parental education in this study was used as a surrogate for socioeconomic status. The level of parental education was high, with only three cases not completing high school. All remaining children had parents who had completed high school or some post secondary education or training. Due to the small number of children with parents that did not complete high school, analyses were conducted with the three outstanding children excluded and then combined with the category of completed high school. Geographical region was considered because of possible different environmental influences across a radius of 100 kilometres.

Data on these variables were missing for at least nine percent of children. The probability of children having some of the symptoms or not was related to whether these variables were missing or not. In particular, the child was less likely to be absent during the winter period, to have a cold, a hoarse voice or a runny nose, if the confounding variables were missing.

For the group of children for whom confounding variable data were available, the presence/absence of symptoms found significant for exposure were further investigated. The proportions of children who experienced the presence of a cold or who were absent from school were examined within strata of the potential confounding and effect modifying variables (Tables 6.4 and 6.5). Raw relative risks for each stratum and crude relative risks and Mantel-Haenszel adjusted relative risks for all strata are displayed. Ninety-five percent confidence intervals are included with all risk estimates.

Table 6.4 Proportions of control and exposed children who experienced non-zero "rates" of school absenteeism stratified by potential confounding and effect modifying variables.

Variable	Exposure	Absence (n)	No absence (n)	Raw relative risk	Crude relative risk (all strata)	Adjusted Mantel-Haenszel relative risk	95% Confidence interval
Age					1.25	1.22	0.97 - 1.53
6 - 8 yrs	Yes	97	48	1.25			0.88 - 1.77
	No	16	14				
9 - 11 yrs	Yes	50	31	1.20			0.89 - 1.61
	No	32	30				
Respiratory illness before age 2					1.25	1.28	1.02 - 1.59
Yes	Yes	25	6	1.21			0.84 - 1.75
	No	12	6				
No	Yes	120	73	1.30			1.00 - 1.69
	No	35	38				
Hayfever					1.28	1.28	1.02 - 1.60
Yes	Yes	23	9	1.44			0.78 - 2.63
	No	6	6				
No	Yes	119	64	1.25			0.98 - 1.59
	No	40	37				
Allergy					1.26	1.26	1.01 - 1.57
Yes	Yes	55	31	1.05			0.75 - 1.48
	No	17	11				
No	Yes	91	47	1.39			1.04 - 1.85
	No	29	32				
Asthma					1.26	1.25	1.00 - 1.55
Yes	Yes	47	20	1.03			0.74 - 1.42
	No	15	7				
No	Yes	100	59	1.36			1.02 - 1.80
	No	32	37				
Parental education					1.25	1.23	0.99 - 1.54
- Completed high school	Yes	29	20	1.18			0.77 - 1.81
	No	15	15				
- Post secondary education	Yes	118	58	1.25			0.97 - 1.63
	No	31	27				
Region					1.35	1.34	1.06 - 1.69
I	Yes	44	24	1.19			0.78 - 1.80
	No	12	10				
II	Yes	38	26	1.60			0.94 - 2.73
	No	10	17				
III	Yes	23	20	1.00			0.65 - 1.55
	No	16	14				
IV	Yes	49	20	1.68			1.05 - 2.70
	No	11	15				

Table 6.5 Proportions of control and exposed children who experienced non-zero "rates" of 'cold' stratified by potential confounding and effect modifying variables.

Variable	Exposure	Colds (n)	No colds (n)	Raw relative risk	Crude relative risk (all strata)	Adjusted Mantel-Haenszel relative risk	95% Confidence interval
Age					1.14	1.11	0.90 - 1.36
6 - 8 yrs	Yes	102	43	1.24			0.89 - 1.73
	No	17	13				
9 - 11 yrs	Yes	49	32	1.01			0.77 - 1.33
	No	37	25				
Respiratory illness before age 2					1.14	1.15	0.95 - 1.40
Yes	Yes	23	8	1.11			0.76 - 1.64
	No	12	6				
No	Yes	126	67	1.16			0.93 - 1.46
	No	41	32				
Hayfever					1.11	1.11	0.92 - 1.34
Yes	Yes	24	8	1.13			0.72 - 1.76
	No	8	4				
No	Yes	121	62	1.11			0.90 - 1.37
	No	46	31				
Allergy					1.12	1.13	0.93 - 1.37
Yes	Yes	56	30	1.07			0.77 - 1.50
	No	17	11				
No	Yes	94	44	1.15			0.91 - 1.46
	No	36	25				
Asthma					1.13	1.12	0.92 - 1.35
Yes	Yes	49	18	1.01			0.75 - 1.35
	No	16	6				
No	Yes	102	57	1.16			0.91 - 1.48
	No	38	31				
Parental education					1.15	1.13	0.92 - 1.37
- Completed high school	Yes	30	19	1.31			0.84 - 2.04
	No	14	16				
- Post secondary education	Yes	120	56	1.07			0.86 - 1.33
	No	37	21				
Region					1.19	1.20	0.99 - 1.46
I	Yes	42	26	1.13			0.74 - 1.73
	No	12	10				
II	Yes	48	16	1.19			0.86 - 1.64
	No	17	10				
III	Yes	27	16	1.11			0.75 - 1.63
	No	17	13				
IV	Yes	44	25	1.38			0.88 - 1.63
	No	12	14				

Differences in raw relative risks within strata suggest that a history of allergy and asthma were associated with less school absenteeism. However, the large width of the 95% confidence intervals suggests that the numbers of children included within strata may have been too small to allow measurement of the magnitude of the association with precision. This may also explain the variability in raw relative risks for school absence between regions. However, there were no observable differences between crude and adjusted relative risks for any variable and the significant association between exposure and absenteeism was maintained.

For the presence of a cold, younger children appeared more at risk than older children, as did children of parents without post-secondary education or from region IV. However, wide confidence intervals create uncertainty about the interpretation of these findings. There were no observable differences between crude and adjusted relative risks for any variable but the magnitude of the association between exposure and the presence of a cold was reduced across all variables and failed to reach statistical significance. However the crude and adjusted relative risks were positive for all variables, suggesting a positive association between exposure and the proportion of children with non-zero "rates" for the presence of a cold. Lack of statistical significance may have been associated with inadequate power due to the exclusion of students for whom potential confounding and effect modifying variable data were missing.

With the inclusion of all hypothesised confounding variables in a logistic model, the presence of absenteeism remained significantly associated with exposure. The only variable that actually affected the presence of absenteeism significantly was the presence of severe chest illness before the age of two (Table 6.6). No significant interactions were observed between exposure and a history of asthma, severe chest illness before the age of 2, hay fever or allergy.

For this group of children, there was no significant relationship between any measured variable and the probability of having a cold.

The findings of the stratified and logistic analyses were unchanged when the three children whose parents did not complete high school were combined with the category of children whose parents did complete high school.

Table 6.6 Adjusted odds ratios for exposure and a series of hypothesised confounding variables for the proportions of children with non-zero "rates" for school absence (n=297)♦

Variable	Coefficient (+SE)	Odds ratios	95% confidence interval
Exposed	0.635 (+ 0.295)	1.89	1.06 - 3.36
Age	–0.002 (+ 0.285)	1.00	0.57 - 1.74
Resp. illness before age 2	0.899 (+ 0.431)	2.46	1.06 - 5.72
Hayfever	0.152 (+ 0.411)	1.16	0.52 - 2.61
Allergies	–0.094 (+ 0.299)	0.91	0.51 - 1.64
Asthma	0.152 (+ 0.327)	1.16	0.61 - 2.21
Completed high school	–0.290 (+ 0.288)	0.75	0.43 - 1.31
Region 1	0.014 (+ 0.351)	1.01	0.51 - 2.02
Region 2	–0.329 (+ 0.350)	0.72	0.36 - 1.43
Region 3	–0.236 (+ 0.364)	0.79	0.39 - 1.61

♦ Derived from a logistic regression model in which the dependent variable was absenteeism. NB. 15% of children could not be included in this analysis because of lack of information about confounders.

For the group of children for whom confounding variable data were available, the non-zero "rates" of symptoms found significantly different for exposure were further investigated. The non-zero "rates" for sore throat and cough with phlegm were examined within strata of the potential confounding and effect modifying variables (Tables 6.7 and 6.8). There was a consistent trend suggesting an association between exposed children and a higher non-zero "rate" of sore throat within all strata. Within the exposed group of children, the non-zero "rates" were higher in those with a history of severe chest illness before the age of two and allergy than in those with no such history. However, the wider confidence intervals for children with a positive past history associated with small numbers suggests there is inadequate power to

Table 6.7 Geometric mean values for the natural log of "rates" of sore throat (excluding individuals with zero "rates") between the exposed and control children, stratified by potential confounding and effect modifying variables

	Exposed children			Control children		
	Rate	n	95% confidence interval	Rate	n	95% confidence interval
Age						
6 - 8 yrs	0.049	96	0.041 - 0.058	0.034	17	0.020 - 0.056
9 - 11 yrs	0.045	59	0.036 - 0.057	0.036	42	0.029 - 0.047
Respiratory illness before the age of 2						
Yes	0.060	25	0.041 - 0.090	0.040	12	0.024 - 0.072
No	0.045	128	0.038 - 0.052	0.035	46	0.027 - 0.045
Hayfever						
Yes	0.047	23	0.033 - 0.066	0.035	8	0.020 - 0.059
No	0.045	124	0.039 - 0.053	0.037	50	0.029 - 0.047
Allergy						
Yes	0.059	60	0.046 - 0.075	0.036	21	0.025 - 0.052
No	0.041	94	0.035 - 0.049	0.036	35	0.027 - 0.049
Asthma						
Yes	0.050	46	0.038 - 0.066	0.039	11	0.021 - 0.072
No	0.046	109	0.039 - 0.054	0.035	48	0.028 - 0.045
Parental education						
- Completed high school	0.054	28	0.039 - 0.074	0.050	21	0.038 - 0.066
- Post secondary education	0.046	127	0.039 - 0.054	0.030	36	0.022 - 0.041
Region						
I	0.047	51	0.037 - 0.060	0.032	12	0.019 - 0.054
II	0.049	39	0.036 - 0.067	0.036	16	0.022 - 0.059
III	0.043	25	0.027 - 0.067	0.039	22	0.027 - 0.056
IV	0.053	48	0.042 - 0.066	0.044	17	0.029 - 0.069

Table 6.8 Geometric mean values for the natural log of "rates" of cough with phlegm (excluding individuals with zero "rates") between the exposed and control children, stratified by potential confounding and effect modifying variables

	Exposed children			Control children		
	Rate	n	95% confidence interval	Rate	n	95% confidence interval
Age						
6 - 8 yrs	0.076	87	0.063 - 0.092	0.055	18	0.035 - 0.087
9 - 11 yrs	0.064	42	0.046 - 0.089	0.056	31	0.041 - 0.078
Respiratory illness before the age of 2						
Yes	0.091	20	0.061 - 0.136	0.051	12	0.031 - 0.086
No	0.069	108	0.057 - 0.083	0.055	36	0.041 - 0.075
Hayfever						
Yes	0.085	22	0.051 - 0.142	0.074	9	0.045 - 0.120
No	0.067	101	0.056 - 0.081	0.053	40	0.039 - 0.071
Allergy						
Yes	0.072	55	0.053 - 0.098	0.072	16	0.045 - 0.116
No	0.071	73	0.059 - 0.086	0.050	32	0.036 - 0.069
Asthma						
Yes	0.084	39	0.063 - 0.113	0.081	12	0.042 - 0.157
No	0.067	90	0.055 - 0.082	0.050	37	0.038 - 0.065
Parental education						
- Completed high school	0.069	29	0.048 - 0.099	0.054	19	0.035 - 0.084
- Post secondary education	0.073	100	0.060 - 0.088	0.054	29	0.039 - 0.075
Region						
I	0.076	41	0.058 - 0.100	0.044	9	0.025 - 0.076
II	0.079	42	0.059 - 0.108	0.076	13	0.045 - 0.129
III	0.078	21	0.050 - 0.124	0.060	17	0.036 - 0.100
IV	0.071	36	0.050 - 0.102	0.036	12	0.021 - 0.063

understand the true significance of these differences. A consistent trend of higher non-zero "rate" of cough with phlegm in the exposed than in control children was also found within all strata. The non-zero "rate" of cough with phlegm was noticeably higher in exposed children with a history of severe chest illness before the age of two than in exposed children with no such history. This was associated with no observable difference in the non-zero "rates" of control children with and without a history of such illness. Also, the non-zero "rates" among controls with a history of hay fever, allergy and asthma was higher than control children with no such history. However, for the reasons described above for sore throat, the significance of these differences remains uncertain.

The non-zero "rates" of sore throat and cough with phlegm were investigated for confounding and effect modification using multiple linear regression. After the inclusion of all variables in the model, sore throat remained significant for exposure. The only variable that significantly affected sore throat was a past history of allergy (Figure 6.9). No significant interactions were observed between exposure and a history of asthma, severe chest illness before the age of two, hay fever or allergies. For this group of children, there was no significant relationship between any measured variable and the probability of a higher "rate" of cough with phlegm.

Table 6.9 Ninety-five percent confidence intervals for exposure and a series of hypothesised confounding and effect modification variables for non-zero "rates" of sore throat

Variable	B Coefficient (+SE)	Exp (B)	95% confidence interval
Exposed	0.301 (+ 0.150)	1.35	1.01 - 1.81
Age	0.035 (+ 0.046)	1.03	0.95 - 1.13
Resp. illness before age 2	0.098 (+ 0.181)	1.10	0.77 - 1.57
Hay fever	–0.202 (+ 0.193)	0.82	0.67 - 1.19
Allergy	0.307 (+ 0.144)	1.36	1.02 - 1.81
Asthma	–0.028 (+ 0.158)	0.97	0.71 - 1.32
Parental education level	–0.268 (+ 0.153)	0.76	0.66 - 1.03
Region	–0.012 (+ 0.054)	0.99	0.89 - 1.09

The findings of the stratified and regression analyses were unchanged when the three children whose parents did not complete high school were combined with the category of children whose parents did complete high school.

Pre-winter heating period

Health data prior to the introduction of winter heating (week 4) were available for all 105 control children and 237 exposed children. Seven exposed children joined the study after week 3. Health data during this period were again compared between the control and exposed children.

The proportions of children with non-zero "rates" are shown in Table 6.10 and the geometric mean "rates" of the control and exposed children, with non-zero "rates" for each symptom, are shown in Table 6.11. No significant differences were found for any symptom, although the non-zero "rates" for dry cough and wheeze approached significance. These results revealed no pattern of higher symptom rates in one group over another prior to the winter heating period.

Table 6.10 Proportion of exposed and control children with non-zero symptom "rates" for each symptom prior to the winter heating period

Symptom	Control (n = 105)	Exposed (n = 244)
Hoarse voice	0.16	0.16
Sore Throat	0.38	0.40
Cough with phlegm	0.28	0.24
Dry cough	0.40	0.43
Sneeze	0.35	0.32
Stopped up nose	0.44	0.46
Runny nose	0.53	0.46
Wheeze	0.12	0.11
'Cold'	0.45	0.35
Absent from school	0.26	0.19

Table 6.11 Geometric mean values for the natural log of individual symptom "rates" (excluding individuals with zero "rates" for each symptom) between the exposed and control children prior to the winter heating period

Symptom	Control mean	Exposed mean
Hoarse voice	0.058 (n=17)	0.066 (n=37)
Sore Throat	0.077 (n=40)	0.082 (n=95)
Cough with phlegm	0.113 (n=29)	0.129 (n=57)
Dry cough	0.087 (n=42)	0.121 (n=101)
Sneeze	0.100 (n=37)	0.099 (n=77)
Stopped up nose	0.125 (n=46)	0.111 (n=109)
Runny nose	0.103 (n=56)	0.105 (n=108)
Wheeze	0.076 (n=13)	0.123 (n=27)
'Cold'	0.079 (n=47)	0.104 (n=84)
Absent from school	0.054 (n=27)	0.047 (n=44)

Dose-response relationships

For symptoms found to vary significantly with exposure, a dose-response effect was explored between symptom presence/absence and the mean 6-hour NO_2 levels as well as between non-zero "rates" and the mean 6-hour NO_2 levels recorded over the winter heating period. Only children from non-gas homes were included in this analysis. Children from gas homes were excluded because home monitoring was limited, making it impossible to estimate accurately the mean home exposure over the winter heating period. Classrooms, on the other hand, were monitored extensively over winter, allowing the mean levels in each classroom over this period to be used as an estimation of dose.

Logistic regression analysis, performed between symptom presence/absence for absenteeism and cold, and recorded NO_2 in all classrooms, revealed a small dose-response effect of borderline significance for the presence of a cold (Table 6.12). The estimated odds ratio of having a non-zero "rate" of cold for an increase of 0.05 ppm of NO_2 was 1.49. Borderline significance was lost when gas classrooms only were considered. No significant dose response effects were found for absenteeism.

Table 6.12 Odds ratios for the proportion of non-zero "rates" of a cold and absenteeism versus NO_2 level (ppm) experienced over the winter heating period for all classrooms♦

Symptom	B coefficients (+SE) (n=264)	Odds ratio for an ↑ of 0.05 ppm	95% confidence interval
'Cold'	8.00 (+ 4.34)	1.49	0.97 - 2.28 (*)
Absenteeism	6.50 (+ 4.08)	1.38	0.93 - 2.06

♦ Children from homes with gas appliances have been excluded from the regression analyses.
(*) p=0.06

Linear regression analyses, performed between log (non-zero) symptom "rates" for sore throat and cough with phlegm, and NO_2 levels, both in all classrooms and in gas classrooms alone, revealed no significant dose-response effects.

Sensitivity analyses were conducted between control and exposed children to investigate the dose-response relationship based on the daily levels experienced by children at school and at home. Children from gas schools and homes were allocated to one of five exposure categories, namely > 0.02 - 0.04 ppm, > 0.04 - 0.06 ppm, > 0.06 - 0.08 ppm, > 0.08 - 0.10 ppm, and > 0.10 ppm. Each classroom was allocated to a category by the occurrence of 6-hour average levels exceeding the lower limit of the category on at least five days and not exceeding its upper limit on more than five days. Home levels were allocated to a category by the mean timed-average measured for each home. The highest of these two allocations was used to determine each child's category of classification. The Student's t-test was then used to compare overall and non-zero symptom "rates" between control children and the exposed children in each category. The proportion of children who experienced each symptom were also compared using relative risk estimates.

Statistically significant differences in the overall "rates" of sore throat, cough with phlegm, the presence of a cold and absenteeism were found between the control and exposed children above 0.08 ppm (Table 6.13).

However, the rates for these four symptoms were higher than the control "rates" across all five categories of exposure. This suggests that appreciable excess symptomatology occurred at levels below 0.08 ppm. Lack of statistically significant differences at the lower levels of exposure may have been due to inadequate power to detect such differences due to the smaller numbers of children in these categories. These results are consistent with the earlier findings of significant differences in these symptoms above 0.04 ppm. Although not reaching statistical significance, there is a notable rise in "rates" of dry cough, sneezing, stopped up nose and runny nose above 0.10 ppm. High "rates" of dry cough and nasal symptoms in the 0.06 to 0.08 ppm category need to be regarded with caution due to the small number (n=12) of children involved. These results suggest that higher "rates" of sore throat, cough with phlegm, cold and absenteeism occurred at low levels of NO_2 exposure and that a dose-response occurred at higher levels.

Statistically significant differences in the proportion of children who experienced a cold or were absent from school were found between the control and exposed children above 0.10 ppm (Table 6.14). However, the proportions were higher in the exposed than control children in all categories of exposure for the presence of a cold and absenteeism. Again, inadequate power due to small numbers of children at lower levels of exposure may explain a lack of statistically significant differences. A dose-response is suggested by the rise in the proportions of children who experienced a cold and absenteeism above 0.06 ppm, acknowledging that less precision is likely between 0.06 and 0.08 ppm due to the inclusion of only 12 children. Consistent trends were not found for the proportions of children who experienced hoarse voice, sneezing, runny nose or wheezing. The statistically significant finding of a lower proportion of control children with stopped up nose between 0.02 and 0.04 ppm and higher proportion of exposed children with hoarse voice between 0.06 and 0.08 ppm is likely to be explained by small sample size.

Table 6.13 Geometric mean values for the natural log of individual symptom "rates" (plus one) between the controls and the exposed children classified into categories based on their highest daily average exposure experienced either at school or at home

Symptom	Controls n = 105	> 0.02 - 0.04 (ppm) n = 47	> 0.04 - 0.06 (ppm) n = 46	> 0.06 - 0.08 (ppm) n = 12	> 0.08 - 0.10 (ppm) n = 94	> 0.10 (ppm) n = 92
Hoarse voice	0.008	0.008	0.015	0.021	0.010	0.020
Sore throat	0.033	0.050	0.040	0.036	0.041	0.054 ($p < 0.01$)
Cough with phlegm	0.037	0.055	0.053	0.053	0.062 ($p = 0.02$)	0.067 ($p = 0.02$)
Dry cough	0.068	0.052	0.070	0.078	0.075	0.088
Sneeze	0.027	0.025	0.024	0.032	0.024	0.039
Stopped up nose	0.053	0.027 ($p = 0.02$)	0.062	0.090	0.042	0.057
Runny nose	0.078	0.074	0.057	0.096	0.067	0.087
Wheeze	0.007	0.023	0.015	0.010	0.018	0.016
'Cold'	0.041	0.081 ($p = 0.02$)	0.064	0.058	0.071 ($p < 0.01$)	0.068 ($p = 0.01$)
Absent from school	0.014	0.023	0.022	0.023	0.022 ($p = 0.03$)	0.028 ($p < 0.01$)

Table 6.14 Proportion of exposed and control children with non-zero symptom "rates" for each symptom. The exposed children are classified into categories based on their highest daily average exposure experienced either at school or at home

Symptom	Controls n = 105	> 0.02 - 0.04 (ppm) n = 47	> 0.04 - 0.06 (ppm) n = 46	> 0.06 - 0.08 (ppm) n = 12	> 0.08 - 0.10 (ppm) n = 94	> 0.10 (ppm) n = 92
Hoarse voice	0.21	0.23	0.22	0.58 (RR = 2.78) 95% CI: 1.52 - 5.10	0.31	0.25
Sore throat	0.64	0.64	0.52	0.75	0.66	0.74
Cough with phlegm	0.49	0.60	0.59	0.42	0.61	0.55
Dry cough	0.66	0.53	0.76	0.58	0.71	0.72
Sneeze	0.48	0.36	0.41	0.58	0.43	0.44
Stopped up nose	0.59	0.34 (RR = 0.58) 95% CI: 0.38 - 0.89	0.57	0.67	0.57	0.58
Runny nose	0.75	0.60	0.63	0.83	0.66	0.67
Wheeze	0.12	0.15	0.22	0.17	0.22	0.16
'Cold'	0.55	0.60	0.59	0.67	0.65	0.71 (RR = 1.28) 95% CI: 1.03 - 1.59
Absent from school	0.47	0.51	0.52	0.58	0.60	0.73 (RR = 1.56) 95% CI: 1.23 - 1.98

Table 6.15 Geometric mean values for the natural log of individual symptom "rates" (excluding individuals with zero "rates" for each symptom) between the controls and the exposed children classified into categories based on their highest daily average exposure experienced either at school or at home

Symptom	Controls	> 0.02 - 0.04 (ppm)	> 0.04 - 0.06 (ppm)	> 0.06 - 0.08 (ppm)	> 0.08 - 0.10 (ppm)	> 0.10 (ppm)
Hoarse voice	0.029 (n=22)	0.023 (n=11)	0.042 (n=10)	0.028 (n=7)	0.024 (n=29)	0.027 (n=23)
Sore throat	0.038 (n=67)	0.056 (n=30) (p=0.05)	0.055 (n=24)	0.039 (n=9)	0.044 (n=62)	0.052 (n=68) (p=0.04)
Cough with phlegm	0.054 (n=51)	0.072 (n=28)	0.064 (n=27)	0.099 (n=5)	0.073 (n=57)	0.085 (n=51) (p=0.02)
Dry cough	0.072 (n=69)	0.067 (n=25)	0.066 (n=35)	0.077 (n=7)	0.069 (n=67)	0.082 (n=66)
Sneeze	0.038 (n=49)	0.043 (n=17)	0.039 (n=19)	0.038 (n=7)	0.034 (n=40)	0.061 (n=40) (p=0.03)
Stopped up nose	0.064 (n=62)	0.058 (n=16)	0.069 (n=26)	0.074 (n=8)	0.049 (n=54)	0.060 (n=53)
Runny nose	0.067 (n=79)	0.094 (n=28)	0.056 (n=29)	0.073 (n=10)	0.070 (n=62)	0.088 (n=62)
Wheeze	0.049 (n=13)	0.069 (n=7)	0.043 (n=10)	0.055 (n=2)	0.038 (n=21)	0.072 (n=15)
'Cold'	0.060 (n=58)	0.094 (n=28) (p=0.05)	0.076 (n=27)	0.065 (n=8)	0.080 (n=61)	0.068 (n=65)
Absent from school	0.024 (n=49)	0.031 (n=24)	0.033 (n=24)	0.035 (n=7)	0.029 (n=56)	0.028 (n=67)

Statistically significant differences in non-zero "rates" of sore throat, cough with phlegm and sneezing were found between control and exposed children above 0.10 ppm (Table 6.15). However, the non-zero "rates" for sore throat and cough with phlegm were higher across all categories for exposed children than for controls. Chance effects associated with small numbers are the likely explanation for the statistically significant difference found for the presence of a cold between 0.02 and 0.04 ppm. No other trends were noted.

The results of these sensitivity analyses, allowing for the lower number of children included in the lower exposure categories, are consistent with the earlier significant findings of increased sore throat, cough with phlegm, cold and absenteeism above 0.04 ppm, and of appreciable symptomatology below 0.04 ppm. They also suggest a dose-response effect may be present at levels above 0.08 ppm.

DISTRIBUTIONS OF RESPIRATORY EPISODES

The distributions of the total number of respiratory episodes among the 105 control and 244 exposed children are shown in Figure 6.3. This pattern was similar to that found in a study of Adelaide children.[87] These distributions show that only small percentages of children experienced no episodes, with the highest number of children experiencing 1 to 4 episodes during the winter season. However, examination of the distributions by type of episode revealed a large number of children did not experience the more severe kinds of episodes. The distributions for *lower respiratory tract - cough with phlegm* highlight this (Figure 6.4).

Analysis, therefore, was again conducted in two parts. Firstly, the proportions of children having each type of respiratory episode were compared between being exposed or a control. Secondly, a comparison was made of the non-zero episode "rates" for each type of episode between the two groups.

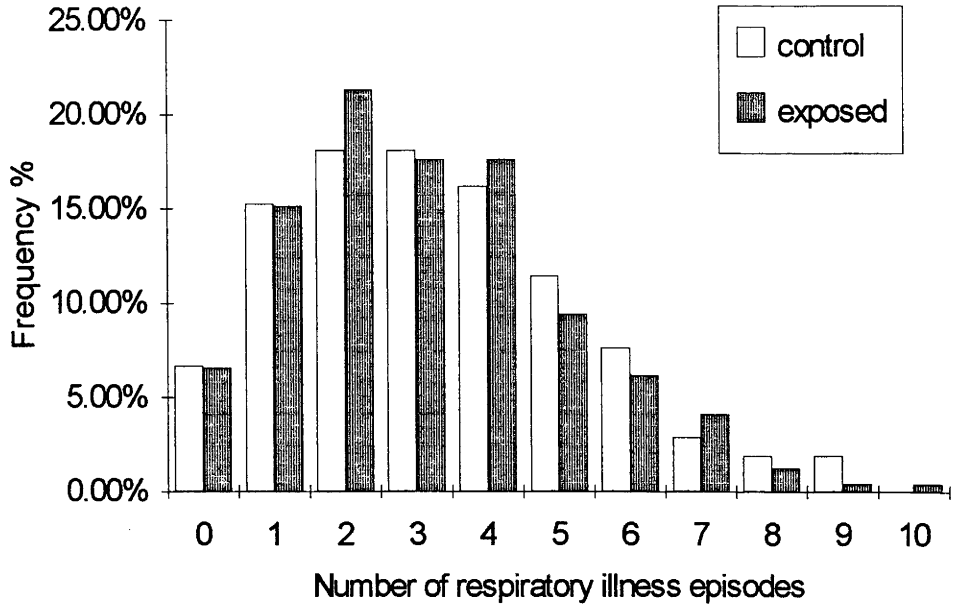


Figure 6.3 Frequency (%) distribution of the number of respiratory illness episodes by classification of exposure

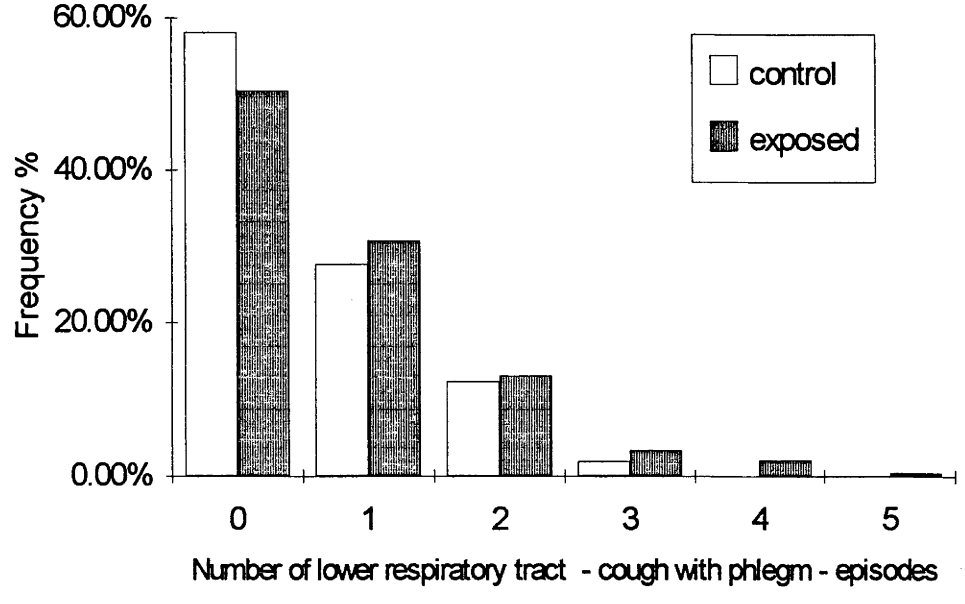


Figure 6.4 Frequency (%) distribution of the number of *lower respiratory tract - cough with phlegm* episodes by classification of exposure

Analysis of episode presence/absence and non-zero episode "rates"

No significant differences were found for the proportion of children with non-zero "rates" for any type of respiratory episode (Table 6.16).

Table 6.16 Proportion of exposed and control children with non-zero episode "rates" for each episode type.

Respiratory episode	Control (n = 105)	Exposed (n = 244)
Upper	0.85	0.81
Lower respiratory tract - cough with phlegm	0.42	0.50
Lower respiratory tract - wheezing	0.12	0.19

The geometric mean "rates" for the control and exposed children, with non-zero "rates" for each type of respiratory episode, are shown in Table 6.17. The "rate" for *lower respiratory tract - cough with phlegm* was significantly higher among the exposed than control children, but the reverse was true for upper respiratory tract episodes. Thus exposure was not associated with an increased incidence of episodes but with an increase in their severity.

Non-zero episode "rates" were also compared following the separate inclusion of the children of uncertain classification. When included as both 'exposed' and 'controls', the significance for *lower respiratory tract - cough with phlegm* was unaffected.

Table 6.17 Geometric mean values for the natural log of individual episode "rates" (excluding individuals with zero "rates" for each episode type) between the exposed and control children

Respiratory episode	Control mean	Exposed mean
All	0.030 (n=98)	0.031 (n=228)
Upper	0.027 (n=89)	0.022 (n=197)*
Lower respiratory tract - cough with phlegm	0.012 (n=44)	0.015 (n=121)*
Lower respiratory tract - wheezing	0.016 (n=13)	0.015 (n=46)

* $p \leq 0.05$

Multivariate analysis

For the group of children on whom confounding data were available, the non-zero "rates" of upper respiratory tract and *lower respiratory tract - cough with phlegm* episodes were further investigated. Non-zero "rates" were examined within strata of potential confounding and effect modifying variables (Table 6.18 and 6.19). There was a consistent pattern within strata of higher non-zero "rates" of upper respiratory tract episodes among control than exposed children, and of higher non-zero "rates" of *lower respiratory tract - cough with phlegm* episodes among exposed than control children. These differences were not statistically significant, with overlapping 95% confidence intervals within all strata.

After the inclusion of the exposure variable and all potential confounding and effect modifying variables with multiple linear regression, no significant relationship was found between any measured variable and the probability of a higher "rate" of *lower respiratory tract - cough with phlegm*.

Dose-response relationship

Sensitivity analyses were conducted between control and exposed children to investigate the dose-response relationships for upper respiratory tract and *lower respiratory tract - cough with phlegm* episodes based on the daily levels experienced by children at school and at home (Table 6.20). The non-zero "rates" of upper respiratory tract episodes were higher in the control than exposed children across all levels of exposure, and statistically significantly lower in exposed children below 0.06 ppm. The non-zero "rates" for *lower respiratory tract - cough with phlegm* episodes were the same between control and exposed children below 0.08 ppm, above which there was a statistically significantly higher "rate" in those exposed. This suggests that there is an effect between *lower respiratory tract - cough with phlegm* episodes

Table 6.18 Geometric mean values for the natural log of "rates" of upper respiratory tract episodes (excluding individuals with zero "rates") between the exposed and control children, stratified by potential confounding and effect modifying variables

	Exposed children			Control children		
	Rate	n	95% confidence interval	Rate	n	95% confidence interval
Age						
6 - 8 yrs	0.022	120	0.020 - 0.025	0.028	29	0.023 - 0.032
9 - 11 yrs	0.022	62	0.018 - 0.026	0.024	50	0.020 - 0.028
Respiratory illness before the age of 2						
Yes	0.020	27	0.016 - 0.026	0.023	18	0.017 - 0.032
No	0.022	153	0.020 - 0.025	0.026	60	0.022 - 0.030
Hayfever						
Yes	0.022	28	0.018 - 0.028	0.027	11	0.018 - 0.040
No	0.022	146	0.020 - 0.025	0.024	66	0.021 - 0.028
Allergy						
Yes	0.023	73	0.020 - 0.026	0.027	24	0.021 - 0.034
No	0.021	109	0.019 - 0.024	0.024	52	0.020 - 0.028
Asthma						
Yes	0.023	56	0.019 - 0.027	0.024	20	0.019 - 0.031
No	0.022	126	0.019 - 0.024	0.025	58	0.022 - 0.029
Parental education						
- Completed high school	0.023	42	0.019 - 0.028	0.026	26	0.021 - 0.033
- Post secondary education	0.022	140	0.019 - 0.024	0.025	49	0.021 - 0.029
Region						
I	0.023	57	0.019 - 0.027	0.026	18	0.020 - 0.035
II	0.022	54	0.018 - 0.026	0.023	21	0.018 - 0.030
III	0.020	31	0.016 - 0.025	0.028	25	0.021 - 0.036
IV	0.023	55	0.019 - 0.028	0.028	25	0.022 - 0.036

Table 6.19 Geometric mean values for the natural log of "rates" of *lower respiratory tract - cough with phlegm* episodes (excluding individuals with zero "rates") between the exposed and control children, stratified by potential confounding and effect modifying variables

	Exposed children			Control children		
	Rate	n	95% confidence interval	Rate	n	95% confidence interval
Age						
6 - 8 yrs	0.015	74	0.013 - 0.017	0.012	13	0.010 - 0.014
9 - 11 yrs	0.012	36	0.010 - 0.015	0.013	29	0.011 - 0.015
Respiratory illness before the age of 2						
Yes	0.015	16	0.011 - 0.019	0.012	10	0.009 - 0.016
No	0.014	93	0.012 - 0.015	0.013	32	0.011 - 0.014
Hayfever						
Yes	0.015	18	0.012 - 0.019	0.014	7	0.010 - 0.020
No	0.014	86	0.012 - 0.015	0.012	35	0.011 - 0.014
Allergy						
Yes	0.014	46	0.012 - 0.016	0.013	14	0.010 - 0.016
No	0.014	63	0.012 - 0.016	0.012	28	0.011 - 0.014
Asthma						
Yes	0.015	28	0.012 - 0.018	0.014	7	0.009 - 0.021
No	0.014	82	0.012 - 0.015	0.012	35	0.011 - 0.014
Parental education						
- Completed high school	0.014	27	0.012 - 0.017	0.013	18	0.011 - 0.016
- Post secondary education	0.014	83	0.012 - 0.016	0.012	24	0.011 - 0.014
Region						
I	0.015	38	0.012 - 0.019	0.010	8	0.009 - 0.013
II	0.017	33	0.015 - 0.020	0.013	9	0.009 - 0.017
III	0.012	19	0.010 - 0.016	0.014	16	0.011 - 0.017
IV	0.014	31	0.012 - 0.016	0.012	11	0.010 - 0.015

Table 6.20 Geometric mean values for the natural log of upper respiratory tract and *lower respiratory tract - cough with phlegm* episode "rates" (excluding individuals with zero "rates" for each episode) between the controls and the exposed children classified into categories based on their highest daily average exposure experienced either at school or at home

Episode	Controls	> 0.02 - 0.04 (ppm)	> 0.04 - 0.06 (ppm)	> 0.06 - 0.08 (ppm)	> 0.08 - 0.10 (ppm)	> 0.10 (ppm)
Upper respiratory tract	0.027 (n=89)	0.019 (n=31) p=0.003	0.019 (n=36) p=0.006	0.024 (n=9)	0.023 (n=81)	0.023 (n=71)
Lower respiratory tract - cough with phlegm	0.012 (n=44)	0.013 (n=21)	0.012 (n=25)	0.012 (n=5)	0.016 (n=47) p=0.02	0.016 (n=44) p=0.01

and exposure, but that the effect may occur at a level higher than the 0.04 ppm previously determined. However, the small numbers of children involved below 0.08 ppm may also be responsible for the lack of effect at lower levels. The significantly lower "rates" for upper respiratory tract episodes in exposed than control children at low levels of exposure suggests the possibility of a physiological response to low levels of exposure that may in some way be protective for upper respiratory tract episodes.

Duration of episodes

The geometric mean duration of episodes are shown in Table 6.21. There were no statistically significant differences between the control and exposed children for all or each type of episode. However, there was a trend for a longer duration of both types of lower respiratory tract episodes among the exposed children.

Table 6.21 Geometric mean values for the natural log of the duration of episodes between the control and exposed children*

Duration (days)	Control mean	Exposed mean
All	6.2	7.0
Upper	4.8	4.6
Lower respiratory tract - cough with phlegm	9.0	10.4
Lower respiratory tract - wheezing	8.7	10.5

* No differences were statistically significant

COUGH WITH PHLEGM EPISODES

In light of the significantly higher non-zero "rate" of *lower respiratory tract - cough with phlegm* episodes described above, another type of episode - *cough with phlegm only* - was defined, independently of the above, to examine the extent of cough with phlegm in the formation of lower respiratory tract episodes. This type required the presence of cough with phlegm on at least two consecutive days, ending with the occurrence of at least two cough with phlegm-free days. Episode duration was again defined as the number of days from onset of symptoms to the last day on which symptoms occurred before the

occurrence of two symptom-free days. This type of episode, then, required the inclusion of cough with phlegm on at least every other day. "Rates" for each child were again obtained by dividing the number of episodes by the number of days of observation. The geometric mean non-zero "rates" and duration for the control and exposed children, for this type of episode, are shown in Table 6.22.

Table 6.22 Geometric mean values for the natural log of individual *cough with phlegm only* "rates" and duration (excluding individuals with zero "rates") between the exposed and control children

Cough with phlegm only episodes	Control mean (n=45)	Exposed mean (n=130)
"Rate"	0.013	0.016 **
Duration (days)	4.5	5.2

** $p < 0.01$

The "rate" of *cough with phlegm only* episodes was statistically significantly higher among exposed than control children. There was no statistical difference in the duration of these episodes between the two groups.

For the group of children on whom confounding data were available, the non-zero "rates" of *cough with phlegm only* episodes were further investigated. Non-zero "rates" were examined within strata of potential confounding and effect modifying variables (Table 6.23). There was a consistent pattern within strata of higher non-zero "rates" of *cough with phlegm only* episodes among exposed than control children. These differences remained statistically significant within a number of strata, with non-overlapping 95% confidence intervals. Small numbers in some cells were associated with wide confidence intervals, indicating inadequate power to determine statistical differences within some strata with precision.

Table 6.23 Geometric mean values for the natural log of "rates" of *cough with phlegm only* episodes (excluding individuals with zero "rates") between the exposed and control children, stratified by potential confounding and effect modifying variables

	Exposed children			Control children		
	Rate	n	95% confidence interval	Rate	n	95% confidence interval
Age						
6 - 8 yrs	0.016	82	0.014 - 0.018	0.012	17	0.009 - 0.015
9 - 11 yrs	0.016	37	0.013 - 0.019	0.013	27	0.010 - 0.016
Respiratory illness before the age of 2						
Yes	0.018	20	0.014 - 0.024	0.012	11	0.009 - 0.014
No	0.015	98	0.014 - 0.017	0.013	32	0.011 - 0.015
Hayfever						
Yes	0.018	20	0.014 - 0.023	0.016	9	0.010 - 0.024
No	0.015	93	0.014 - 0.017	0.012	35	0.010 - 0.014
Allergy						
Yes	0.016	49	0.014 - 0.019	0.015	15	0.011 - 0.019
No	0.015	69	0.013 - 0.017	0.012	28	0.010 - 0.014
Asthma						
Yes	0.017	38	0.014 - 0.021	0.017	11	0.011 - 0.028
No	0.015	81	0.013 - 0.017	0.012	33	0.010 - 0.013
Parental education						
- Completed high school	0.015	27	0.012 - 0.018	0.014	15	0.011 - 0.017
- Post secondary education	0.016	92	0.014 - 0.018	0.012	28	0.010 - 0.014
Region						
I	0.017	40	0.014 - 0.021	0.010	8	0.009 - 0.010
II	0.016	40	0.014 - 0.019	0.016	12	0.010 - 0.024
III	0.015	19	0.011 - 0.020	0.014	15	0.011 - 0.017
IV	0.017	31	0.013 - 0.021	0.011	10	0.009 - 0.012

After controlling for potential confounding and effect modifying variables using linear regression, the "rate" of *cough with phlegm only* episodes remained statistically significantly higher among those exposed. Asthma was the only variable to significantly affect these episodes (Table 6.24).

Table 6.24 Confounding variables found significant for non-zero "rates" for *cough with phlegm only* episodes

Variable	B Coefficient (+SE)	Exp (B)	95% confidence interval
Exposed	0.182 (+ 0.092)	1.20	1.01 - 1.44
Asthma	0.189 (+ 0.094)	1.21	1.00 - 1.45

Sensitivity analysis was conducted between control and exposed children to investigate the dose-response relationship for non-zero "rates" of *cough with phlegm only* episodes based on the daily levels experienced by children at school and at home (Table 6.25). The "rate" was higher among the exposed than control children across all categories of exposure. There was a statistically higher "rate" and a suggested dose-response above 0.08 ppm.

Table 6.25 Geometric mean values for the natural log of *cough with phlegm only* episode "rates" (excluding individuals with zero "rates") between the controls and the exposed children classified into categories based on their highest daily average exposure experienced either at school or at home

Episode	Controls	> 0.02 - 0.04 (ppm)	> 0.04 - 0.06 (ppm)	> 0.06 - 0.08 (ppm)	> 0.08 - 0.10 (ppm)	> 0.10 (ppm)
Cough with phlegm only	0.013 (n=45)	0.015 (n=25)	0.014 (n=24)	0.014 (n=5)	0.016 (n=53) p=0.03	0.019 (n=48) p=0.002

SUMMARY

The "rates" of sore throat, cough with phlegm, wheeze, cold and absenteeism were statistically significantly higher among exposed than control children. Cold and absenteeism differences were found to be due to higher proportions of non-zero "rates" among those exposed. Sore throat and cough with phlegm, however, were explained by higher non-zero "rates" among those

exposed. Wheezing was unable to be explained by either process, but the proportion of children with non-zero "rates" was higher in the exposed group. The levels of significance for these variables increased when the group of children of uncertain classification were included as exposed. After controlling for potential confounding and effect modifying variables, sore throat and cough with phlegm remained significant. A small dose response effect based on the mean 6-hour average classroom level recorded over the winter heating period was found for cold only. Results of sensitivity analyses conducted at different categories of exposure based on the maximum daily levels experienced by children at school and at home showed higher "rates" at low levels of exposure and demonstrated a dose-response above 0.08 ppm.

The proportion of children with non-zero episode "rates" for each type of episode was the same among control and exposed children. However, "rates" of upper respiratory tract episodes were significantly higher among controls, while "rates" of *lower respiratory tract - cough with phlegm* and *cough with phlegm only* episodes were significantly higher among those exposed. The "rate" of *cough with phlegm only* remained significant after controlling for potential confounding and effect modifying variables. Sensitivity analyses showed an increase in *lower respiratory tract - cough with phlegm* and *cough with phlegm only* episodes at levels above 0.08 ppm. The mean duration of episodes for different episode types were not statistically different between groups. However, there was a trend for the duration of all types of lower respiratory tract episodes to be longer among the exposed than control children.

Overall, a clear association was revealed between exposure to low levels of indoor nitrogen dioxide and different aspects of respiratory illness. A detailed interpretation of this association is provided in Chapter 7.

CHAPTER 7

DISCUSSION

The NO_2 levels recorded in this study are of public health concern, with children being exposed, in schools and homes, to levels of NO_2 that substantially exceeded current air quality guidelines. As described in Chapter 5, the maximum hourly concentrations found in unflued gas classrooms exceeded the WHO's recommended goal on twenty-three percent of measured days, and the daily timed-average concentrations exceeded this goal in nine percent of gas appliance homes. Since many Australian schools and homes have similar types of appliances, these levels of exposure are likely to have been experienced by many children and adults elsewhere. Such exposures are likely to continue if appropriate intervention does not occur.

Intervention, however, may be costly and slow to introduce. As mentioned in Chapter 2, even after guidelines about adequate classroom ventilation were distributed to schools using unflued gas heaters, still thirty percent of school rooms had recorded levels of NO_2 that exceeded current guidelines. To modify or replace existing heaters would be costly. Co-operation would be required between consumers, health authorities and the gas industry. As an interim measure, however, efforts need to be directed to education of school authorities and householders to ensure correct maintenance of unflued gas appliances and to educate users about the effects of ventilation procedures. This is a public health issue that needs to be addressed through both national and state public health agencies.

However, the problem may be more serious. The WHO's air quality standards are 0.08 ppm over twenty-four hours and 0.21 ppm over one hour for ambient NO_2 exposure.[9] As described in chapter 2, the one hour goal was selected to allow a margin of safety below the controlled human exposure level

of 0.3 ppm, identified as the "lowest-observed-effect-level" in asthmatic subjects. The twenty-four hour goal was set to avoid the occurrence of repeated exposures approaching this level, and to create a margin of safety against chronic effects. These guidelines were set after consideration of animal, controlled human exposure and epidemiological studies. Few epidemiological studies involving objective measurements of NO_2 were available at the time the goals were set. However, in those studies with measured NO_2 levels, mixed results were found for the association between exposure and effect (Table 2.4) at levels below these standards.

The NHMRC's acceptance of 0.3 ppm hourly average as a level of concern was also based largely upon the findings of controlled human exposure studies. While subjects in these studies experienced levels of NO_2 in a fashion akin to receiving spike concentrations for up to four hours, exposures were not recurrent over time and were not necessarily associated with exposure to infectious agents at the time of the experiment.

The United States Environmental Protection Agency (EPA) has set a standard of 0.053 ppm averaged over one year.[10] The EPA points out that, while it is not possible to quantify the margin of safety provided by this standard, the level has been set to allow an adequate margin of safety against long term effects and to provide some protection against possible short term effects. This standard, however, does not address the occurrence of repeated short term, spike concentrations of NO_2.

This study, unlike past epidemiological studies, has measured daily spike levels of NO_2. The exposure measurements were developed purposely to reflect short-term exposures in light of animal studies which found adverse mortality effects for animals challenged with bacteria after exposure. While

most animal studies used NO_2 exposure levels above those normally experienced by humans, one study[44] used an urban pattern of exposure with low levels of NO_2 and a 4:1 ratio of spike to background level. A significant increase in mortality was found in the spike exposed group. The background levels found in the present study were lower than those used in the animal experiment, but the ratio of spike to background level was of the same order or greater than the ratio used.

In this context of large spike to background ratios, exposure to NO_2 at what have been thought to be relatively safe levels was associated with a significant increase in sore throat, cough with phlegm, the presence of a cold and absenteeism from school. As well, lower respiratory tract episodes involving cough with phlegm were significantly associated with exposure. This association occurred with mean daily timed-average levels of exposure to NO_2 that exceeded 0.04 ppm.

Two apparently independent processes were seen to account for the symptom findings. One was the proportion of children affected, the other was the "rate" in those affected. Exposure was associated with a higher proportion of children who experienced cold and absenteeism, but the "rates" in those affected were similar. On the other hand, exposure was associated with higher non-zero "rates" for sore throat and cough with phlegm, but the proportions affected were similar. Exposed children were thus more likely to have a cold or be absent, and, when affected, were likely to suffer more with sore throat or cough with phlegm than controls.

When respiratory episodes were the item of analysis, it was seen that total episode incidence was similar in the two groups. However, different "rates" emerged for different types of episodes. Upper respiratory tract episodes were significantly more frequent among controls, while lower respiratory tract episodes involving cough with phlegm were significantly more frequent among

those exposed. Thus, of those who became ill, exposed children were more likely to experience more serious episodes involving the lower respiratory tract. There was also a trend towards longer duration of lower respiratory tract episodes among those exposed, although this did not reach statistical significance.

This study adds new information about exposure patterns in humans that need to be considered in standard setting. The protocols used in past epidemiological studies have not incorporated spike patterns of NO_2 as measures of exposure. They relied mainly on average levels of NO_2 experienced over one to two weeks and produced mixed results. These studies are important because they allow associations between quantified total dose exposure and health effects to be explored. However the occurrence of spike exposures is not necessarily reflected in the average concentration. Misclassification of spike exposures based on cumulative measures may have been one explanation for the mixed results found in past studies.

The level and pattern of exposure found significant in this study add another dimension for consideration. Our exposed subjects were exposed to spikes of the order of 0.08 ppm or greater against a background of 0.02 ppm and were associated with adverse health effects. This pattern of spike to background exposure, that is a 4:1 ratio, was found to be associated with increased toxicity in animal studies over a wide range of background NO_2 concentrations. Perhaps this pattern of exposure also influences toxicity over a wide range of concentrations in humans. If so, the setting of a single air quality standard for spike exposures would be difficult. Whatever the mechanism of toxicity, the pattern of morbidity and levels of exposure in this study suggest that the WHO's guideline of 0.21 ppm and the NHMRC's level of 0.3 ppm over one hour are too high.

Multivariate analyses

The questionnaire used to gather data about potential confounding and effect modifying variables was long, and not all were completed or returned by parents. It is interesting that the resultant missing data for confounding variables was associated with less reported symptoms. This may indicate that parents who failed to provide background data may have been less likely to record symptoms accurately. Nevertheless, after controlling for confounding in those children on whom data were available, absenteeism from school, sore throat, and *cough with phlegm only* episodes were clearly associated with exposure to NO_2. However, the association found between exposure and cough with phlegm and presence of a cold, as well as between exposure and lower respiratory tract - cough with phlegm episodes, remains less clear. After controlling for confounding in those children on whom data were available, no significant associations were found between any measured variable and these three factors. There are at least three explanations for this. Since data on confounding variables were missing for some children, reduced power due to less numbers, or bias in the missing data, may have been responsible. Stratified analyses did not demonstrate the presence of confounding.

Severe chest illness before the age of two was found to be associated with absenteeism. This finding is consistent with children who experienced such chest illness being predisposed to respiratory or other problems likely to result in more absenteeism. This finding, however, did not alter the significant association found between NO_2 exposure and absenteeism. Although parental education level and allergy were associated with sore throat, neither affected the association found for exposure.

Asthma was found to be significantly associated with *cough with phlegm only* episodes. Since asthma is associated with cough and noisy breathing, it is possible that some parents interpreted this as cough with phlegm, even in the

absence of productive cough. Nevertheless, asthma did not confound or modify the association found between exposure and *cough with phlegm only.*

Magnitude of the effect

The effects at the individual level were not trivial. For example, an average exposed child experienced 6.2 days of cough with phlegm symptoms during the winter heating period compared to 3.7 days for an average control child (Table 6.1). When considered over, say, a school community of 10,000 children, this equates to a morbidity burden of 62,000 person symptom days of cough with phlegm during winter among those exposed compared to 37,000 person symptom days among controls. Similar extrapolation to 10,000 children would be associated with approximately 25,000 absentee days in those exposed compared to 14,000 in controls over the winter heating period, an excess of 11,000 school days. When it is considered that the exposure appears to affect especially the lower respiratory tract, it seems likely that doctor visits and medication, and their attendant costs, could also be affected.

It was noted earlier that children from gas heated classrooms with daily measured average nitrogen dioxide levels less than 0.04 ppm constituted an uncertain exposure group, because of their exposure to the products of unflued gas combustion. However, when these children were included in the analysis as 'exposed', the level of statistical significance for conditional "rates" of sore throat, cough with phlegm and a cold increased. When included as 'controls', the level of significance diminished. This suggests that appreciable symptomatology occurred with exposure to very low levels of NO_2 in that group. However, an effect due to other unmeasured products of gas combustion, especially nitrous acid (HNO_2), cannot be excluded. Gas combustion indoors results in the formation of HNO_2[88] and health effects can occur as a result of the dose of hydrogen ion received from HNO_2.[38]

Outdoor monitoring was suggested by Dr Ryan. Its purpose was to understand if background effects, rather than exposure to NO_2 indoors, might have been responsible for symptom production in children. Since outdoor levels of NO_2 were shown to be uniformly low, it is unlikely that they contributed to high levels of symptomatology in any child. Moreover, since outdoor NO_2 levels are mainly produced by vehicular emissions, the uniformly low levels across all schools suggest that other vehicular co-pollutants were unlikely to be the cause of the observed differences.

Using the mean 6-hour average levels of NO_2 experienced over the winter heating period as an index of dose, a dose-response effect was found for only one symptom. When maximum daily averages were used in a sensitivity analysis, there was a suggestive dose-response above 0.08 ppm for the symptoms and episodes found significant for exposure.

Bias

Parents were told about the nature and purpose of the study at the outset, to counter any ethical concerns involving their children. As well, the non-response and drop out rates in this study were high. The possibility existed, then, that the information given to parents may have somehow influenced participation and/or symptom reporting. However, parental knowledge did not appear to influence selectively the non-response or drop out rate, which were similar between gas heated and electrically heated schools. This view was strengthened by the lack of significant differences in symptomatology between control and exposed children prior to the winter heating period, at a time when NO_2 levels in all schools were similar. This suggests that selection bias was unlikely to be responsible for any differences found during the study period.

The methods used to manufacture and analyse monitors used in this study have been shown to have an accuracy of within 10% of

chemiluminescent analysers.[77] While the use of static placement of monitors in classrooms may have introduced error in relation to the personal dose, the levels recorded were an accurate reflection of the classroom concentrations of NO_2 experienced by each child.

Misclassification has been a criticism of many past studies. The extent of monitoring undertaken in this study was designed to allow accurate classification of subjects. Children remained in the same classroom on each school day for the entire study period. These classrooms were monitored extensively. Misclassification of children based on classrooms levels was unlikely. Resource limitations meant that home monitoring was limited in each household. As a result, 36 children whose home levels remained less than the classification criterion level could not be classified as exposed. Since these children may have experienced higher levels at other times, their exclusion avoided possible misclassification. Possible misclassification due to within-home variation of NO_2 levels was dealt with by the use of a personal monitoring technique. Children were required to wear badge monitors pinned to their outer clothing during times of monitor exposure. This removed the need for activity data about children and accurately recorded the personal exposure levels of NO_2 experienced by each child during the monitored time period.

The retrospective collection of symptom data using questionnaires has been a criticism of past studies. This relates to the reporting bias involved in trying to remember past health information, often over the previous twelve months or longer. While the use of prospective symptom data collection in this study, using daily diaries, may have allowed a selective increase in symptom reporting by parents of children exposed to gas appliances, it may equally have permitted the detection of symptom differences that would otherwise have been lost due to the effects of recall bias.

The determination of respiratory illness episodes was based on symptom data collected using daily diaries. The validity of this approach was investigated by Samet and colleagues[89] who compared a similar symptom-based classification of respiratory episodes with diagnoses made by nurse practitioners and by the subjects' own physicians. Symptom collection in their study differed from the method used in this study. Mothers were telephoned every two weeks to ascertain the symptom occurrence during the previous two weeks. However, the method of recording by parents on the diaries was comparable. Also the age of the children in the two studies differed, which may have affected the comparability of symptom reporting. Samet et. al. found that the method of classification of episodes was sensitive to, but not specific for detecting lower respiratory tract illness. Most of the lower respiratory illness classified as false positives involved "wet cough" which is equivalent to "cough with phlegm" in this study. This led to the stratification of lower respiratory illness into illness with "wet cough" alone and "wheezing". If the low specificity found by Samet et al. is consistent in this study, it would most likely have diminished the likelihood of finding that lower respiratory tract illness was associated with NO_2 exposure. The fact that a positive result was found is therefore noteworthy.

The possibility exists that children in the two groups of schools were exposed to different microbial epidemiology. However, this seems unlikely since the paired schools were close geographically and there were a large number of different classrooms included in the study. This view was strengthened by the negligible between-subject dependence, due to the use of cluster sampling, found at the classroom level, and the similarity in total respiratory episode "rates" between the exposed and control children. The differences observed were particularly in relation to severity and duration.

Conclusion

Increased "rates" of respiratory symptoms were associated with daily exposure to indoor levels of nitrogen dioxide greater than 0.04 ppm. Had this figure been averaged over a full twenty-four hours, including periods when children were not exposed to gas, the level would have been lower still. This is considerably lower than the WHO recommended level, and indicates that a review of the daily exposure level goal for indoor NO_2 is warranted.

In such a review, a one-hour goal also needs to be considered. As described in Chapter 5, the one hour maximum concentrations were approximately twice the six-hour levels. This ratio suggests a one-hour maximum goal for NO_2 should be at least twice a twenty-four hour recommended goal, allowing for periods of non-gas exposure over twenty-four hours. However, the ratio also implies that the maximum hourly concentrations involved, which were greater than 0.08 ppm, were associated with six-hour levels greater than 0.04 ppm. Since levels above 0.04 ppm were found to be significantly associated with illness, this suggests that a maximum one-hour goal of 0.08 ppm of NO_2 should be considered for school classrooms. Without a knowledge of the ratio of maximum hourly levels to average levels over different times of gas exposure, it is unwise to extrapolate the relationship of 0.08 ppm of NO_2 to a one-hour maximum goal for twenty-four hours.

However, this study raises another issue about goal levels. Exposure to NO_2 was seen to occur, more often than not, over periods of time greater than one hour and less than twenty-four hours. Measurements were taken only during periods of gas exposure, and were likely to reflect spike levels that occurred on a daily basis. Exposure based on such levels was associated with increased illness. This raises an important question about the most appropriate duration and circumstances of sampling in relation to goal setting. A new goal with a timed period of, say, six to eight hours, may be appropriate. Perhaps

monitoring should be restricted to periods of gas use in gas appliances environments. Since this is the first study of its kind, replication studies are needed. Goal levels should be based on the results of further studies in which monitoring can reflect spike exposures. This would better reflect the usual exposure patterns experienced in human environments during periods of high exposure. Future goals notwithstanding, the results of this study suggest that the ultimate goal is the lowest possible NO_2 emission from gas appliances.

The future

This study focussed on NO_2, yet other atmospheric pollutants exist and may be associated with disease. It will be important, as technology becomes available, to measure all likely pollutants in the one setting, and to determine their independent and interactive effects. As well, more epidemiological studies are required that focus on daily spike levels of exposure. Since health effects at the individual level are not huge, study designs that allow inter-study comparison and integration of results across different environments would also be appropriate. Ideally, these issues would best be addressed by effective international collaboration between appropriate environmental agencies.

APPENDIX 1

Mean twenty-four badge and average atmospheric concentrations (ppm) per child measured in the 1991 pilot study

Electrically heated school		Unflued gas heated school	
Mean 24 hour badge conc.	Mean average atmospheric 24 hour conc.	Mean 24 hour badge conc.	Mean average atmospheric 24 hour conc.
0.245	0.007	0.303	0.008
0.250	0.007	0.228	0.006
0.105	0.003	0.330	0.009
0.113	0.003	0.430	0.009
0.103	0.003	1.533	0.042
0.098	0.003	0.268	0.007
0.148	0.004	0.560	0.015
0.100	0.003	0.513	0.014
0.098	0.003	0.563	0.011
0.065	0.002	0.705	0.010
0.088	0.002	0.668	0.018
0.123	0.003	0.768	0.021
0.250	0.005	0.573	0.012
0.160	0.004	0.900	0.018
0.143	0.003	0.890	0.024
0.105	0.003		
0.270	0.007		
0.207	0.004		
0.193	0.004		
0.147	0.003		
0.190	0.005		
0.158	0.004		
0.155	0.004		
0.108	0.003		

APPENDIX 2

Mean school-time and non-school-time badge and average atmospheric concentrations (ppm) per child measured during the 1991 pilot study.

Electrically heated school			
Mean school-time badge conc.	Mean average atmospheric school-time conc.	Mean non-school-time badge conc.	Mean average atmospheric non-school-time conc.
0.067	0.007	0.058	0.002
0.015	0.002	0.088	0.003
0.028	0.003	0.180	0.007
0.083	0.009	0.048	0.002
0.085	0.009	0.158	0.006
0.010	0.001	0.210	0.008
0.030	0.003	0.100	0.004
0.043	0.005	0.153	0.006
0.078	0.008	0.067	0.002
0.023	0.003	0.165	0.006
0.035	0.004	0.133	0.005
0.055	0.006	0.157	0.006*
0.048	0.005	0.118	0.004
0.045	0.005	0.293	0.011*
0.053	0.006	0.158	0.006
0.053	0.006	0.263	0.010
0.060	0.007	0.238	0.009
0.055	0.006	0.080	0.003
0.048	0.005	0.088	0.003
0.053	0.006	0.110	0.004
Unflued gas heated school			
Mean school-time badge conc.	Mean average atmospheric school-time conc.	Mean non-school-time badge conc.	Mean average atmospheric non-school-time conc.
0.400	0.044	0.185	0.007
0.440	0.048	0.215	0.008*
0.475	0.052	0.240	0.009
0.333	0.036	0.123	0.004
0.463	0.050	0.155	0.006
0.490	0.053	0.293	0.011
0.458	0.050	0.280	0.010
0.290	0.032	0.215	0.008
0.333	0.036	0.190	0.007
0.515	0.056	0.350	0.013
0.570	0.062	0.230	0.008
0.473	0.051	0.203	0.007
0.280	0.030	0.158	0.006
0.365	0.040	0.290	0.011
0.403	0.044	0.258	0.009
0.333	0.036	0.163	0.006
0.377	0.041	0.180	0.007
0.443	0.048	0.243	0.009
0.278	0.030	0.153	0.006
0.350	0.038	0.203	0.007*

* Denotes the presence of unflued gas appliances at home.

APPENDIX 3

This letter and consent form were sent to parents in February 1992, inviting them to participate in the main study.

Dear Parent/Guardian

We are writing to ask for your assistance in a study of national importance. Overseas reports suggest that indoor air pollution could have a harmful effect on the respiratory systems of children. Our Centre has been asked to study this matter by the National Health and Medical Research Council and we are collecting information from a number of NSW schools. Your child's school is one that has volunteered to take part in the study.

WHAT WOULD BE REQUIRED OF YOU?

1. Your main responsibility would be to keep a simple **daily diary** of your child's respiratory symptoms from April to October. The diary would be supplied by us and would take at most about **1 to 2 minutes a day to fill out**.

2. As well, we would ask you to fill out a **questionnaire** about your child's general health and relevant household factors during the study.

WHAT WOULD BE REQUIRED OF YOUR CHILD?

The air in your child's classroom will be monitored from April to September. There will be **NO** invasive tests given to your child. A **selected group of children** will be required to wear a badge monitor home for **eight evenings only**. Your child may or may not be one of these children.

THIS STUDY WILL HELP US BETTER UNDERSTAND THE EFFECTS THAT INDOOR AIR CONDITIONS HAVE ON THE LUNGS OF OUR CHILDREN AND HOW WE CAN BEST PROTECT THEM. YOU WOULD GENUINELY HELP IN ACHIEVING THIS GOAL.

To take part please complete the consent form on the enclosed sheet and have your child return it to his or her teacher in the envelope provided as soon as possible. You will be contacted soon afterwards.

Yours sincerely,

Professor Robert Douglas
MA (Penn), MD (Adel), FRACP, FRACGP
Director
National Centre for Epidemiology
and Population Health.

Dr. Louis Pilotto
BSc., MBBS(Hons), FRACGP
Program Co-ordinator.

1992 CHILDHOOD RESPIRATORY ILLNESS STUDY

Yes we would like to participate in the indoor air monitoring - respiratory illness study.

CHILD'S FULL NAME:

_____

PARENT/GUARDIAN'S FULL NAME:

_____

ADDRESS FOR CORRESPONDENCE:

_____

_____

POST CODE _____

TELEPHONE: ( ) _____

SCHOOL: _____

_____

WHAT GRADE IS YOUR CHILD IN THIS YEAR? _____

Parent/Guardian's signature: _____

APPENDIX 4

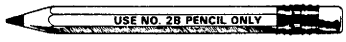
NCEPH 2082

HEALTH STUDY

DAILY HEALTH SYMPTOM DIARY

Please complete this diary at the end of each day including weekend days and holidays. We want to know if your child was bothered by any of these symptoms during the day or the night on each day of the week. Fill in the circle if your child was bothered by the symptom. Leave the circle blank if your child was not bothered by the symptom on a particular day.

PLEASE COMPLETE THE CALENDAR EVERY DAY.



Name

THIS DIARY IS FOR THE WEEK

STARTING		ENDING		ID
	DAY		DAY	
○ Jan		○ Jan		
○ Feb		○ Feb		
○ Mar	0 0	○ Mar	0 0	0 0 0 0
○ Apr	1 1	○ Apr	1 1	1 1 1 1
○ May	2 2	○ May	2 2	2 2 2 2
○ Jun	3 3	○ Jun	3 3	3 3 3 3
○ Jul	4	○ Jul	4	4 4 4 4
○ Aug	5	○ Aug	5	5 5 5 5
○ Sep	6	○ Sep	6	6 6 6 6
○ Oct	7	○ Oct	7	7 7 7 7
○ Nov	8	○ Nov	8	8 8 8 8
○ Dec	9	○ Dec	9	9 9 9 9

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SYMPTOMS	MON	TUE	WED	THU	FRI	SAT	SUN
HOARSE VOICE	○	○	○	○	○	○	○
SORE THROAT	○	○	○	○	○	○	○
COUGH WITH PHLEGM	○	○	○	○	○	○	○
DRY COUGH	○	○	○	○	○	○	○
SNEEZING	○	○	○	○	○	○	○
STOPPED UP NOSE	○	○	○	○	○	○	○
RUNNY NOSE	○	○	○	○	○	○	○
WHEEZING	○	○	○	○	○	○	○
HAS A COLD - Mark circle only if you think your child has a cold today	○	○	○	○	○	○	○
MISSED SCHOOL TODAY due to any of the above symptoms (exclude weekends & holidays)	○	○	○	○	○	○	○
NONE OF THE ABOVE OR HEALTHY – No symptoms	○	○	○	○	○	○	○
– CHILDREN WITH ASTHMA ONLY –							
REGULAR MEDICINE - Did you take your regular asthma medicine today?	○	○	○	○	○	○	○
EXTRA MEDICINE - Did you take extra medicine for asthma today?	○	○	○	○	○	○	○

APPENDIX 5

SHORT QUESTIONNAIRE

CHILD'S ID NUMBER:

CHILD'S SURNAME:

CHILD'S FIRST NAME:

1. What type of stove do you use for cooking on a regular basis?
   (please tick)

   ☐ Electric
   ☐ Gas
   ☐ Other

2. Do you have an exhaust fan above your stove that you use while cooking?
   (please tick)

   ☐ Yes
   ☐ No

3. How is your home heated during winter?
   (please tick)

   ☐ Electric heating
   ☐ Natural gas heating
   ☐ LPG heating
   ☐ Wood heating
   ☐ Other

4. If a gas heater is used is it vented or flued to the outside?
   (please tick)

   ☐ Yes
   ☐ No

5. Does anyone smoke inside your home on a regular basis?
   (please tick)

   ☐ Yes
   ☐ No

APPENDIX 6

National Centre For Epidemiology and Population Health

The Australian National University

RESPIRATORY ILLNESS — NITROGEN DIOXIDE STUDY: Children's Questionnaire

Dear Parent/Guardian

Your child's school is one of a number of NSW schools participating in a major research study into the effects of indoor air pollution on the respiratory health of children. This study is being conducted by the National Centre for Epidemiology and Population Health of the Australian National University and has the approval of the Catholic Education Office of your Archdiocese. It is supported by the National Health and Medical Research Council.

To obtain information on your child's respiratory health and the factors that affect it, we would appreciate your co-operation in completing this questionnaire. Because the questionnaire is designed for analysis by computer, it is important you read and follow the instructions on the next page carefully.

ALL INFORMATION IN THIS STUDY WILL BE KEPT CONFIDENTIAL AND USED ONLY FOR RESEARCH. Once you have completed the questionnaire, please return it in the reply-paid envelope provided (no stamp required) as soon as possible.

Thank you for your help.

Robert Douglas
Director

Louis Pilotto
Co-Principal Researcher

PLEASE PRINT

CHILD'S NAME

CHILD'S SCHOOL

STREET ADDRESS

CHILD'S GRADE THIS YEAR

CITY, STATE, POSTAL CODE

CHILD'S TEACHER

( )
PHONE NUMBER

PARENTS' FULL NAMES

CHILD'S ID NUMBER

PLEASE READ THE INSTRUCTIONS ON THE REVERSE SIDE OF THIS PAGE BEFORE COMPLETING THIS QUESTIONNAIRE

2887

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THIS QUESTIONNAIRE IS DESIGNED TO BE READ BY AN OPTICAL SCANNER. IN ORDER TO BE SCANNED ACCURATELY IT IS IMPORTANT THAT THE INSTRUCTIONS BE OBSERVED.

- **Use a No. 2B pencil ONLY. Do not use ink, ballpoint pens or felt tip markers.**
- **Completely fill the oval with a heavy dark mark.**
- **Cleanly erase any answer you wish to change.**
- **Do not make any stray marks on the form. Where spaces for written answers appear, it is necessary to stay within the borders of the provided box.**
- **Do not use STAPLES, PINS, PAPER CLIPS, TAPE or LIQUID PAPER on this form.**
- **Do not TEAR or CUT any portion of the form. Do not FOLD this document.**

Please review these samples provided.

CHILD'S PERSONAL DATA

1. **What is this child's sex?**
   ● Female ○ Male (THE CHILD IS FEMALE.)
2. **What is this child's date of birth?**
   9 – 1 – 82 (CHILD'S DATE OF BIRTH IS JANUARY 9, 1982.)
   DAY MONTH YEAR
3. **What is this child's age?**
   10 (CHILD IS 10 YEARS OLD.)
4. **What is this child's ethnic background?**
   ● Australian (Aboriginal)
   ○ Australian (Non-Aboriginal)
   ○ Other – SPECIFY:
   (THE CHILD IS OF AUSTRALIAN ETHNIC BACKGROUND.)

9. **Was your child seen by a doctor or other health practitioner for a severe chest illness AFTER the age of 2 years?**
   ○ No ■ Yes
   ○ Don't know **IF YES:**

   A. **Did the child have more than one such illness?**
      ○ No ○ Yes

   B. **What was the diagnosis?**
      MARK ALL THAT APPLY.
      ⊘ Pneumonia ○ Croup
      ⊖ Bronchiolitis ⊜ Asthma
      ⊘ Bronchitis ○ Don't know
      ■ Other – SPECIFY:
      (THESE ARE INCORRECT MARKS.)

   C. **Was the child kept in the hospital overnight for any such illness?**
      ○ No ○ Yes

CHILD'S PERSONAL DATA

1. **What is this child's sex?**
   ○ Female ○ Male

2. **What is this child's date of birth?**
   __ – __ – ____
   DAY MONTH YEAR

3. **What is this child's age?**

4. **What is this child's ethnic background?**
   ○ Australian (Aboriginal)
   ○ Australian (Non-Aboriginal)
   ○ Other – SPECIFY:

5. **What is today's date?**
   __ – __ – ____
   DAY MONTH YEAR

CHILD'S MEDICAL HISTORY

The questions in this section apply to the past medical history of your child. In general, we are asking you to recall events that may have occurred several years ago. If you cannot remember or were not living with the child during the time periods in question, please indicate that by filling in the "Don't know" oval.

6. **What did this child weigh when he or she was born?**
   ○ Under 1,500 grams (under 3 lbs 5 ozs)
   ○ 1,500 - 2,500 grams (3 lbs 5 oz - 5 lbs 8 ozs)
   ○ Over 2,500 grams (over 5 lbs 8 oz)
   ○ Don't know

7. **When the child was born, was he or she kept in the hospital after the mother went home?**
   ○ No ■ Yes
   ○ Don't know
   IF YES:

   A. **Was the child born prematurely?**
      ○ No ○ Yes
   B. **Was the child kept in an Intensive Care Unit?**
      ○ No ○ Yes
   C. **Did this child have to have a ventilator or have a tube put in to help breathing?**
      ○ No ○ Yes
   D. **How long did this child need oxygen while in the hospital?**
      ○ Not at all
      ○ For less than two weeks
      ○ For two to four weeks
      ○ For a month or more
   E. **Did this child need oxygen at home after leaving the hospital?**
      ○ No ○ Yes

8. **Was your child seen by a doctor or other health practitioner for a severe chest illness BEFORE the age of 2 years?**
   ○ No ■ Yes
   ○ Don't know
   IF YES:

   A. **Did the child have more than one such illness?**
      ○ No ○ Yes
   B. **What was the diagnosis?**
      MARK ALL THAT APPLY.
      ○ Pneumonia ○ Croup
      ○ Bronchiolitis ○ Asthma
      ○ Bronchitis ○ Don't know
      ■ Other – SPECIFY:
   C. **Was the child kept in the hospital overnight for any such illness?**
      ○ No ○ Yes

9. **Was your child seen by a doctor or other health practitioner for a severe chest illness AFTER the age of 2 years?**
   ○ No ■ Yes
   ○ Don't know
   IF YES:

   A. **Did the child have more than one such illness?**
      ○ No ○ Yes
   B. **What was the diagnosis?**
      MARK ALL THAT APPLY.
      ○ Pneumonia ○ Croup
      ○ Bronchiolitis ○ Asthma
      ○ Bronchitis ○ Don't know
      ■ Other – SPECIFY:
   C. **Was the child kept in the hospital overnight for any such illness?**
      ○ No ○ Yes

10. **Has your child ever had an operation on his or her chest?**
○ No ☐ Yes – SPECIFY:
○ Don't know

11. **Has your child ever had a serious chest injury?**
○ No ☐ Yes – SPECIFY:
○ Don't know

12. **Has a doctor or other health practitioner ever said that your child had heart disease?**
○ No ☐ Yes – SPECIFY:
○ Don't know

13. **Has your child ever had hay fever?**
○ No ☐ Yes
○ Don't know IF YES:

A. **At what age did she or he FIRST have hay fever?**
○ Under 2 years
○ 2 years or older, but before starting grade one
○ In grade one or later
○ Don't know

14. **Has a doctor or other health practitioner ever said that your child had allergies?**
○ No ☐ Yes
○ Don't know IF YES:

A. **To which of the following is she or he allergic?**
MARK ALL THAT APPLY.
○ Things that are eaten or ingested, for example, food or medicine.
○ Things that are breathed in or inhaled, for example, dust, pollens, molds, animal fur or dander, smoke.
○ Things which come in contact with the skin, for example, wool.
☐ Other – SPECIFY:
○ Don't know

15. **Has a doctor or other health practitioner ever said that your child has cystic fibrosis?**
○ No ○ Yes
○ Don't know

CURRENT HEALTH

The questions in the following section apply mainly to current symptoms related to your child's chest. In general, we are asking you to recall events that have occurred over the past twelve months. If you cannot remember or were not living with the child during the time periods in question, please indicate that by filling in the "Don't know" oval.

COUGH

16. **Does this child usually cough first thing in the morning?**
○ No ☐ Yes
○ Don't know IF YES:

A. **Has this cough been present for as much as 3 months in a row out of the year?**
○ No ○ Yes, past twelve months only
○ Yes, past twelve months and other years

17. **Does this child usually cough at other times during the day or night?**
○ No ☐ Yes
○ Don't know IF YES:

A. **Has this cough been present for as much as 3 months in a row out of the year?**
○ No ○ Yes, past twelve months only
○ Yes, past twelve months and other years

PHLEGM

18. **Does this child usually seem congested in the chest or bring up phlegm with colds?**
○ No ○ Yes
○ Don't know

19. **Does this child usually seem congested in the chest or bring up phlegm other than with colds?**
○ No ☐ Yes
○ Don't know IF YES:

A. **Has this congestion or phlegm been present for as much as 3 months in a row out of the year?**
○ No ○ Yes, past twelve months only
○ Yes, past twelve months and other years

OTHER ILLNESS

20. **During the past twelve months, did this child have hay fever?**
○ No ☐ Yes
○ Don't know IF YES:

A. **Was the child seen by a doctor or other health practitioner for hay fever?**
○ No ○ Yes

PAGE 2

21. During the past twelve months, did this child have a runny nose for 3 or more days out of the week for 3 or more months in a row?
○ No ○ Yes
○ Don't know

22. During the past twelve months, was this child seen by a doctor or other health practitioner for an ear infection?
○ No ○ Yes
○ Don't know

23. During the past twelve months, did this child have any chest illness?
○ No ☐ Yes
○ Don't know ⬇ IF YES:

A. Did the child have more than one such illness?
○ No ○ Yes

B. Were the child's activities restricted for three days or more because of any such illness?
○ No ○ Yes

C. Was the child seen by a doctor or other health practitioner for any such illness?
○ No ○ Yes

D. What was the diagnosis?
MARK ALL THAT APPLY.
○ Pneumonia ○ Bronchitis
○ Asthma ○ Don't know
☐ Other – SPECIFY:

E. Did the child take antibiotics for any such illness?
○ No ○ Yes

F. Was the child kept overnight in the hospital for any such illness?
○ No ○ Yes

24. During the past twelve months, did this child have any gastrointestinal illness (i.e., affecting the stomach or intestines)?
○ No ☐ Yes
⬇ IF YES:

A. Did the child have more than one such illness?
○ No ○ Yes

B. Were the child's activities restricted for three days or more because of any such illness?
○ No ○ Yes

C. Was the child seen by a doctor or other health practitioner for any such illness?
○ No ○ Yes

D. What was the diagnosis?

E. Did the child take antibiotics for any such illness?
○ No ○ Yes

F. Was the child kept overnight in the hospital for any such illness?
○ No ○ Yes

25. During the past twelve months, did this child have any OTHER illness?
○ No ☐ Yes
⬇ IF YES:

A. Did the child have more than one such illness?
○ No ○ Yes

B. Were the child's activities restricted for three days or more because of any such illness?
○ No ○ Yes

C. Was the child seen by a doctor or other health practitioner for any such illness?
○ No ○ Yes

D. What was the diagnosis?

E. Did the child take antibiotics for any such illness?
○ No ○ Yes

F. Was the child kept overnight in the hospital for any such illness?
○ No ○ Yes

WHEEZING

26. Has your child's chest ever sounded wheezy or whistling, including times when he or she had a cold?
○ No ○ Yes
○ Don't know

IF NO or DON'T KNOW:
SKIP THE FOLLOWING QUESTIONS ON WHEEZING AND GO DIRECTLY TO THE SECTION ON ASTHMA (QUESTION 38)

27. When was the last time this wheezing occurred?
○ Within the past week
○ Within the past month (but not in the past week)
○ Within the past twelve months (but not in the past month)
○ Since starting first grade (but not in the past twelve months)
○ Age 2 or older, but before starting grade one
○ Under age 2

28. Has your child ever wheezed with colds?
○ No ☐ Yes
⬇ IF YES:

A. Has this occurred in the past twelve months?
○ No ○ Yes

29. Has your child ever wheezed when she or he did not have a cold?
○ No ☐ Yes
⬇ IF YES:

A. Has this occurred in the past twelve months?
○ No ○ Yes

30. **Has your child ever wheezed for 3 or more days out of the week for a month or longer?**
○ No ☐ Yes
IF YES:
A. Has this occurred in the past twelve months?
○ No ○ Yes

31. **During which months of the past twelve months did your child have an episode of wheezing?**
MARK ALL THAT APPLY.
○ January ○ May ○ September
○ February ○ June ○ October
○ March ○ July ○ November
○ April ○ August ○ December
○ Did not occur in the past twelve months

32. **Has your child ever had episodes of shortness of breath with wheezing?**
○ No ☐ Yes
IF YES:
A. Has this occurred in the past twelve months?
○ No ○ Yes

33. **Has your child ever been wakened at night by wheezing?**
○ No ☐ Yes
IF YES:
A. When was the last time this occurred?
○ Within the past week
○ Within the past month (but not in the past week)
○ Within the past twelve months (but not in the past month)
○ Since starting first grade (but not in the past twelve months)
○ Age 2 or older, but before starting grade one
○ Under age 2

34. **Has your child ever required medication for this wheezing?**
○ No ☐ Yes
IF YES:
A. Has this occurred in the past twelve months?
○ No ○ Yes

35. **Has your child ever been seen in a hospital Emergency Room for this wheezing?**
○ No ☐ Yes
IF YES:
A. During the past twelve months, approximately how many times has he or she been seen in an Emergency Room for wheezing?
○ None ○ 7–12
○ 1–2 ○ 12 or more
○ 3–6

36. **Has your child ever been kept overnight in the hospital for this wheezing?**
○ No ☐ Yes
IF YES:
A. When was the last time this occurred?
○ Within the past twelve months
○ Since starting grade one (but not in the past twelve months)
○ Age 2 or older, but before starting grade one
○ Under age 2

37. **Does your child ever have episodes of wheezing after he or she has been playing hard or exercising?**
○ No ○ Yes

ASTHMA

38. **Has a doctor ever said your child had asthma?**
○ No ☐ Yes
○ Don't Know **IF YES:**
A. When was the last time your child took medication for asthma?
○ Within the past week
○ Within the past month (but not in the past week)
○ Within the past twelve months (but not in the past month)
○ Since starting grade one (but not in the past twelve months)
○ Age 2 or older, but before starting grade one
○ Under age 2
○ Never took medication specifically for asthma
B. Which best describes the child's current level of symptoms? Please read all answers before choosing the best response.
○ The child has not been troubled by asthma during the past twelve months
○ The child has had some asthma in the past twelve months, but did not take any medication for it
○ The child has had some asthma in the past twelve months, requiring medication only for occasional episodes
○ The child has had asthma in the past twelve months, requiring medication on a routine basis, but did not have any episodes while on medication
○ The child has had asthma in the past twelve months, requiring medication on a routine basis and also had one or more episodes requiring additional treatment
C. During which months of the past twelve months did your child have an episode of wheezing? MARK ALL THAT APPLY.
○ January ○ May ○ September
○ February ○ June ○ October
○ March ○ July ○ November
○ April ○ August ○ December
○ Did not take any medication for asthma in the past twelve months

HOME CHARACTERISTICS

The questions in this section apply to the home in which the child is currently living.

39. How long has your child lived in this suburb?
- ○ Has lived in the suburb since birth
- ○ Moved here before the age of two
- ○ Moved here when 2 years or older, but before starting grade one
- ○ Moved here in grade one or later
- ○ Don't know

40. How long has your child lived within 25 miles of this suburb?
- ○ Has lived within 25 miles of this suburb since birth
- ○ Moved within 25 miles of this suburb before the age of two
- ○ Moved within 25 miles of this suburb when 2 years or older, but before starting grade one
- ○ Moved within 25 miles of this suburb in grade one or later
- ○ Don't know

41. How long has your child lived in your current residence?
- ○ Has lived in this house since birth
- ○ Moved here before the age of two
- ○ Moved here when 2 years or older, but before starting grade one
- ○ Moved here in grade one or later
- ○ Don't know

42. Which best describes the building in which your child lives? Include all apartments, flats, etc., even if vacant.
- ○ A mobile home or trailer
- ○ A one-family house detached from any other house
- ○ A one-family house attached to one or more houses
- ○ A building for 2 families
- ○ A building for 3 or 4 families
- ○ A building for 5 or more families
- ○ A boat, tent, van
- ☐ Other – SPECIFY:

43. About when was this building originally built? Do not count remodeling, additions, or conversions.
- ○ 1986 or later
- ○ 1980 to 1985
- ○ 1970 to 1979
- ○ 1960 to 1969
- ○ 1950 to 1959
- ○ 1940 to 1949
- ○ 1939 or earlier
- ○ Don't know

44. How many bedrooms do you have?
- ○ No bedroom
- ○ 1 bedroom
- ○ 2 bedrooms
- ○ 3 bedrooms
- ○ 4 bedrooms
- ○ 5 or more bedrooms

45. Do you have any dogs, cats, other furry pets, or birds?
○ No ○ Yes

GAS COOKING

46. Do you have a GAS cooking stove, range or oven?
○ No ○ Yes

IF NO:
SKIP THE FOLLOWING QUESTIONS ON GAS COOKING AND GO DIRECTLY TO THE SECTION ON HOME HEATING (QUESTION 50)

47. Does your gas cooking stove, range or oven have a continuously burning pilot light?
- ○ No
- ○ No, it has an electric starter
- ○ Yes
- ○ Don't know

48. Is there a fan over the gas cooking stove, range or oven, or elsewhere in the kitchen area?
○ No ☐ Yes

IF YES:

A. How does this fan work?
- ○ Kitchen exhaust is vented to the outside
- ○ Fan has a charcoal filter
- ○ Fan recirculates indoor air
- ○ Don't know

B. How often is the fan used?
- ○ Most of the time when stove is in use
- ○ Occasionally
- ○ Rarely or never

49. During the past twelve months, was your gas cooking stove, range or oven used for heating or drying OTHER THAN WHILE COOKING?
- ○ Not at all
- ○ Rarely, once or twice in the past year
- ○ Infrequently, three or more times in the past year, but not as often as once a week
- ○ Occasionally, once a week or so in the past year
- ○ Frequently, most cold winter days in the past year

HOME HEATING

The questions in this section have to do with how you heat your home.

50. How is your home heated?
- ○ Electricity
- ○ Kerosene
- ○ Solar
- ○ Coal
- ○ Natural Gas
- ○ LPG
- ○ Oil
- ○ Wood
- ☐ Other-SPECIFY:

51. If gas heating is used, is the heater flued (vented) or not?
- ○ No
- ○ Yes
- ○ Don't know

52. During the past twelve months, have any of the following been used to heat your home?
MARK AS MANY AS APPLY.
- ○ Wood stove
- ○ Fireplace
- ○ Portable kerosene heater (unvented)
- ○ Portable gas heater (unvented)
- ○ Portable electric heater
- ○ None of the above

AIR CONDITIIONING

53. Does your home or apartment have any air-conditioning?
○ No ☐ Yes
▼ IF YES:

A. Which rooms have air-conditioning?
MARK ALL THAT APPLY.
☐ All rooms (central air-conditioning)
☐ Living or family room
☐ This child's bedroom
☐ Other rooms

B. What type of air-conditioning do you have?
○ Refrigerative ○ Both
○ Evaporative ○ Don't know

C. Does the air-conditioner recirculate indoor air, or bring in fresh air from outside, or both?
○ Recirculates indoor air
○ Brings in outside air
○ Both
○ Don't know

AIR CLEANING DEVICES

54. Do you have any air cleaning devices?
○ No ☐ Yes
▼ IF YES:

A. What types?
MARK ALL THAT APPLY.
○ Filter ○ Charcoal
○ Ion generator ○ Electrostatic precipitator
☐ Other – SPECIFY:

MOISTURE LEVEL

55. Has there ever been water damage to the building or its contents, for example from broken pipes, leaks, or flood?
○ No ☐ Yes
○ Don't know ▼ IF YES:

A. Has there been water damage to the building during the past twelve months?
○ No ○ Yes ○ Don't know

56. Has there ever been mold or mildew on any surfaces (other than food) inside the home?
○ No ☐ Yes
○ Don't know ▼ IF YES:

A. Has there been mold or mildew on any surfaces inside the home during the past twelve months?
○ No ○ Yes ○ Don't know

B. Which rooms have been affected?
○ Bathroom(s)
○ Bedroom(s)
○ Living area(s)
○ Kitchen
○ Attic
○ None of the above

57. Do you use a humidifier? Include any humidifier system built into your heating system.
○ No ☐ Yes
▼ IF YES:

A. What type of humidifier do you use?
MARK ALL THAT APPLY
○ Built into heating system
○ Steam vaporizer
○ Ultrasonic cool mist
○ Spinning disk cool mist
☐ Other – SPECIFY:

FAMILY HISTORY

The questions in this section apply to the child's family history. If you cannot remember or do not know the answer to any of these questions, please fill in the "Don't know" oval.

58. Has a doctor ever said the BIOLOGICAL father of this child had chronic bronchitis, emphysema, or chronic obstructive lung disease?
○ No ○ Yes
○ Don't know

59. Has a doctor ever said the BIOLOGICAL father of this child had asthma?
○ No ○ Yes
○ Don't know

60. Has a doctor ever said the BIOLOGICAL mother of this child had chronic bronchitis, emphysema, or chronic obstructive lung disease?
○ No ○ Yes
○ Don't know

61. Has a doctor ever said the BIOLOGICAL mother of this child had asthma?
○ No ○ Yes
○ Don't know

62. Did this child's mother smoke while she was pregnant with this child?
○ No ☐ Yes
○ Don't know ▼ IF YES:

A. During which part of the pregnancy did she smoke? MARK ALL THAT APPLY.
○ First 3 months
○ Middle 3 months
○ Last 3 months

63. Between the time the child was born and he or she turned two years old, were there any smokers in the household? Include regular visitors, for example grandparents or babysitters.
○ No ☐ Yes
▼ IF YES:

A. Did this child's mother (or stepmother or female guardian) smoke during this period?
○ No ○ Yes

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64. **Between the time the child turned two years old and he or she started first grade, were there any smokers in the household? Include regular visitors, for example grandparents or babysitters.**
○ No ☐ Yes
▼ **IF YES:**
A. Did this child's mother (or stepmother or female guardian) smoke during this period?
○ No ○ Yes

CURRENT HOUSEHOLD MEMBERS

65. **Counting yourself, how many people 14 YEARS OF AGE OR OLDER live in this child's home?**
○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 or more

66. **Not counting yourself, how many people UNDER 14 YEARS OF AGE live in this child's home?**
○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 or more

67. **Not counting yourself, how many people YOUNGER than this child live in this child's home?**
○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 or more

68. **What is your sex?**
○ Female
○ Male

69. **What is your relationship to this child?**
○ Biological parent
○ Adoptive parent
○ Stepparent
○ Grandparent
○ Legal guardian
○ Other primary adult

70. **Is English your primary language?**
○ No ○ Yes

71. **What is the highest grade or educational level you have completed?**
○ Did not complete primary school
○ Completed primary school
○ Completed high school
○ Some college or post-secondary education or training (includes completion of college or graduate work)

72. **Do you currently smoke cigarettes?**
○ No ☐ Yes
▼ **IF YES:**
A. About how many cigarettes do you smoke on average per day INSIDE YOUR HOME?
○ Fewer than 10 ○ 10 to 14 ○ 15 to 24 ○ 25 to 34 ○ 35 to 44 ○ 45 or more

73. **Do you currently smoke pipes or cigars?** MARK ALL THAT APPLY.
○ Pipes
○ Cigars
○ Neither

74. **Is there another primary adult (for example, your spouse or your partner) living in your household?**
○ No ☐ Yes
▼ **IF YES:**
A. What is the highest grade or educational level completed by this other adult?
○ Did not complete primary school
○ Completed primary school
○ Completed high school
○ Some college or post-secondary education or training (includes completion of college or graduate work)
B. Does he or she currently smoke cigarettes?
○ No ☐ Yes
▼ **IF YES:**
C. About how many cigarettes does he or she smoke on average per day inside your home?
○ Fewer than 10 ○ 10 to 14 ○ 15 to 24 ○ 25 to 34 ○ 35 to 44 ○ 45 or more
D. Does he or she currently smoke pipes or cigars? MARK ALL THAT APPLY.
○ Pipes
○ Cigars
○ Neither

75. **Not counting yourself and your spouse or partner, does anyone smoke cigarettes within your home (as opposed to smoking only outside your home)? Include regular visitors, for instance a grandparent or babysitter.**
○ No ☐ Yes
▼ **IF YES:**
A. Counting ONLY these other smokers, about how many cigarettes are smoked PER DAY inside your home?
○ Fewer than 10 ○ 10 to 14 ○ 15 to 24 ○ 25 to 34 ○ 35 to 44 ○ 45 or more

THE FOLLOWING QUESTION ON FAMILY INCOME IS OPTIONAL.

76. **In which of the following ranges did your TOTAL FAMILY INCOME fall for the last year? Include all income, before taxes and deductions, of all members of your family.**
○ Less than $15,000 ○ $15,000 to $29,999 ○ $30,000 to $49,999 ○ Over $50,000 ○ Don't know

THANK YOU FOR COMPLETING THE CHILDREN'S HEALTH STUDY!

COMMENTS

Please use this space if you have any additional comments concerning this health study.

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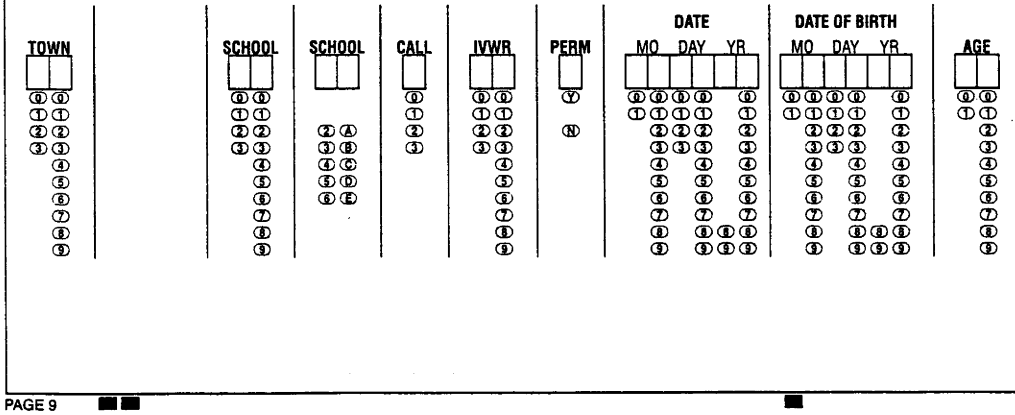
Before sealing the envelope, please check the front of the questionnaire:

- **Have you entered your child's name and address?**

Thank you for your help.

FOR OFFICE USE ONLY



APPENDIX 7

Frequency distribution of 6-hour passive diffusion badge monitor placements in 41 classrooms from 8 schools. Two to three monitors were placed daily in each room.

Electrically heated classrooms			Unflued gas heated classrooms		
School	Classroom	Frequency	School	Classroom	Frequency
1	1	103	2	6	123
	2	104		7	123
	3	104		8	123
	4	103		9	123
	5	105			
3	10	99	4	15	117
	11	99		16	117
	12	96		17	116
	13	97		18	118
	14	98		19	116
				20	116
5	21	95	6	26	127
	22	99		27	128
	23	98		28	131
	24	98		29	130
	25	98		30	129
7	31	100	8	36	127
	32	100		37	127
	33	99		38	123
	34	100		39	126
	35	99		40	126
				41	127

APPENDIX 8

Frequency distribution of hourly passive diffusion badge monitor placements in 41 classrooms from 8 schools. Two to three monitors were placed hourly in each room over a two week period.

Electrically heated classrooms			Unflued gas heated classrooms		
School	Classroom	Frequency	School	Classroom	Frequency
1	1	146	2	6	178
	2	148		7	181
	3	148		8	180
	4	149		9	177
	5	145			
3	10	96	4	15	115
	11	97		16	113
	12	96		17	114
	13	96		18	115
	14	97		19	115
				20	114
5	21	149	6	26	180
	22	149		27	180
	23	153		28	179
	24	148		29	180
	25	152		30	180
7	31	108	8	36	183
	32	108		37	177
	33	108		38	183
	34	105		39	180
	35	110		40	177
				41	179

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